Author:
Gregson, Charlotte H U

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The development of strain-release-driven transformations

1,2-metallate and semipinacol rearrangement reactions

The Development of Strain-Release-Driven Transformations: 1,2-Metallate and Semipinacol Rearrangement Reactions

Charlotte H. U. Gregson

Supervisor: Prof. Varinder K. Aggarwal

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Abstract

Modern approaches to organic synthesis often look to break down target molecules into key molecular fragments. These fragments, or "building blocks", require reactive functional groups that enable the target molecule to be assembled efficiently and selectively through the formation of new C–C or C–heteroatom bonds. This thesis outlines investigations into novel coupling reactions, which harness the inherent strain energy of small-ring cyclic building blocks.

The key reaction mechanisms explored are strain-release-driven 1,2-rearrangement reactions. Firstly, investigations into the 1,2-metallate rearrangement of boronate complexes with an activated cyclopropane α to boron are described (Figure Ia). In addition, the strain-release of azabicyclo[1.1.0]butane was explored as the driving force for the 1,2-metallate rearrangement reaction (Figure Ib). Finally, investigations into a novel strain-release semipinacol rearrangement reaction were undertaken (Figure Ic).

All three reaction mechanisms facilitated the formation of a new C–C bond and provide access to novel molecules with interesting sp^3-rich scaffolds and diverse functionality.

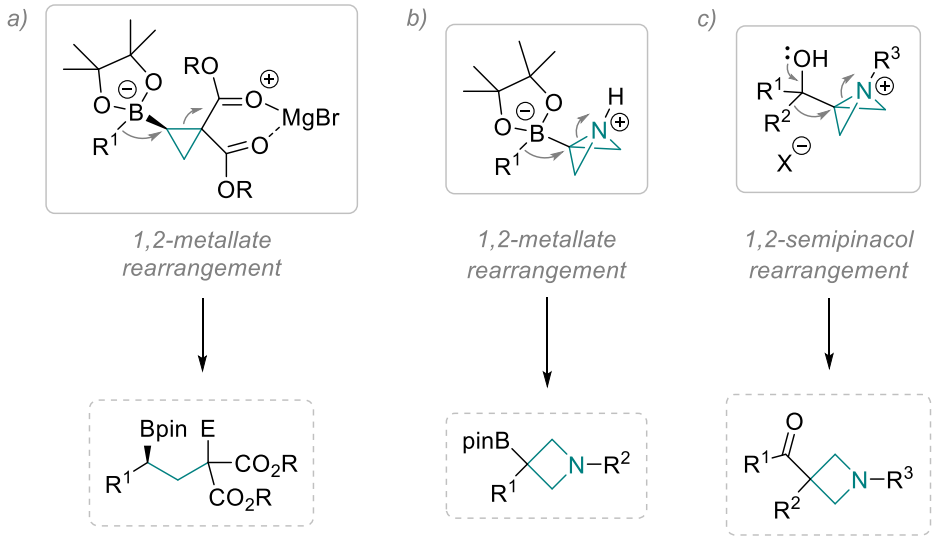

Figure I. Key strain-release-driven reaction mechanisms investigated.

Author's Declaration

"I declare that the work in this dissertation was carried out in accordance with the Regulations of the University of Bristol. The work is original, except where indicated by special reference in the text, and no part of the dissertation has been submitted for any other academic award. Any views expressed in the dissertation are those of the author.

SIGNED: Charlotte Gregson DATE: 14.06.2021"

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Acknowledgements

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The friendships I have made have been the highlight of my PhD studies. I cannot possibly name them all, but I would like to thank the lovely and talented people who have made working in the lab/group parties/the running club such a fun experience.

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Outside of the lab, I want to thank my parents for their endless support, the literal roof over my head, but also for generally being such inspiring people. I also want to thank my sister Flo, for setting the bar high and then encouraging me to reach it. Navigating a PhD was made all the less daunting with Flo going through the same thing in the next building.

Finally, thanks to Tenn for his love, as I would not have been able to complete the PhD without him by my side.

Acronyms and Abbreviations

The ACS standard List of Abbreviations was used with the following additions:

A	electron withdrawing group
ABB	azabicyclo[1.1.0]butane or azabicyclo[1.1.0]butyl
BCB	bicyclo[1.1.0]butane or bicyclo[1.1.0]butyl
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bpin	pinacol (2,3-dimethyl-2,3-butanediol) boronic ester
br.	broad
COD	1,5-cyclooctadiene
Cy	cyclohexyl
D	electron donating group
DA	donor-acceptor
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMPU	*N*,*N*′-dimethylpropyleneurea
dr	diastereomeric ratio
ds	diastereospecificity
E	electrophile
ee	enantiomeric excess
er	enantiomeric ratio
es	enantiospecificity
GCMS	gas chromatography mass spectrometry
h	hours
HATU	hexafluorophosphate azabenzotriazole tetramethyl uranium
KHMDS	potassium bis(trimethylsilyl)amide
LA	Lewis acid
LDA	lithium diisopropylamide
LTMP	lithium tetramethylpiperidide
min	minutes
nbd	2,5-norbornadiene

NBS	*N*-bromosuccinimide
nd	not determined
NOE	nuclear Overhauser effect
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TMEDA	tetramethylethylenediamine
Tol-BINAP	2,2′-Bis(di-p-tolylphosphino)-1,1′-binaphthyl
v/v	volume per volume

1. General introduction

1.1. The concept of strain in organic chemistry

1.1.1. Strain-release as a tool in synthetic chemistry

Strain is a fundamental property of organic molecules; different elements of molecular strain combine to influence bond strengths, molecular conformation and hybridisation. The inherent strain of small cyclic compounds has an immense effect on their reactivity, with strain-release an important driving force for reaction mechanism.

The use of strain-release as a tool in the synthesis of valuable fine chemicals has long been a popular strategy. When considering a retrosynthesis, it is somewhat counterintuitive to reconnect atoms to give strained molecules that undergo strain-release reactions in the forward sense. However, one can select common strained building blocks, with predictable, selective strain-release reactivity as convenient synthons. The further development of strain-release methodology from these key strained molecular building blocks will continue to unlock this modern approach to organic synthesis.

1.1.2. Elements of strain in cyclic molecules

The concept of ring strain was first introduced by Baeyer in 1885 who hypothesised that 3- and 4-membered ring-containing alicyclic molecules would be less stable than acyclic analogues.[1] This instability arises from the requirement that the bond angles deviate from the ideal 109° of a tetrahedron (Figure 1a). This theory of bond-angle strain (or Baeyer strain) is indeed correct, however, Baeyer incorrectly deduced that rings with greater than 5 ring atoms would also experience bond-angle strain because of the assumption that the rings would be planar.[2] We now know that cyclic molecules can adopt puckered conformations to relieve bond-angle strain. The primary example being cyclohexane, which adopts the chair geometry to achieve internal bond angles of 109°.

However, alicyclic molecules with greater than 6 ring atoms do in fact have higher ring strain but not for the reasons Baeyer proposed. This is because the inherent strain of cyclic molecules is comprised not only bond-angle strain but also torsional strain (or Pitzer strain) and trans-annular strain (or Prelog strain).[2]

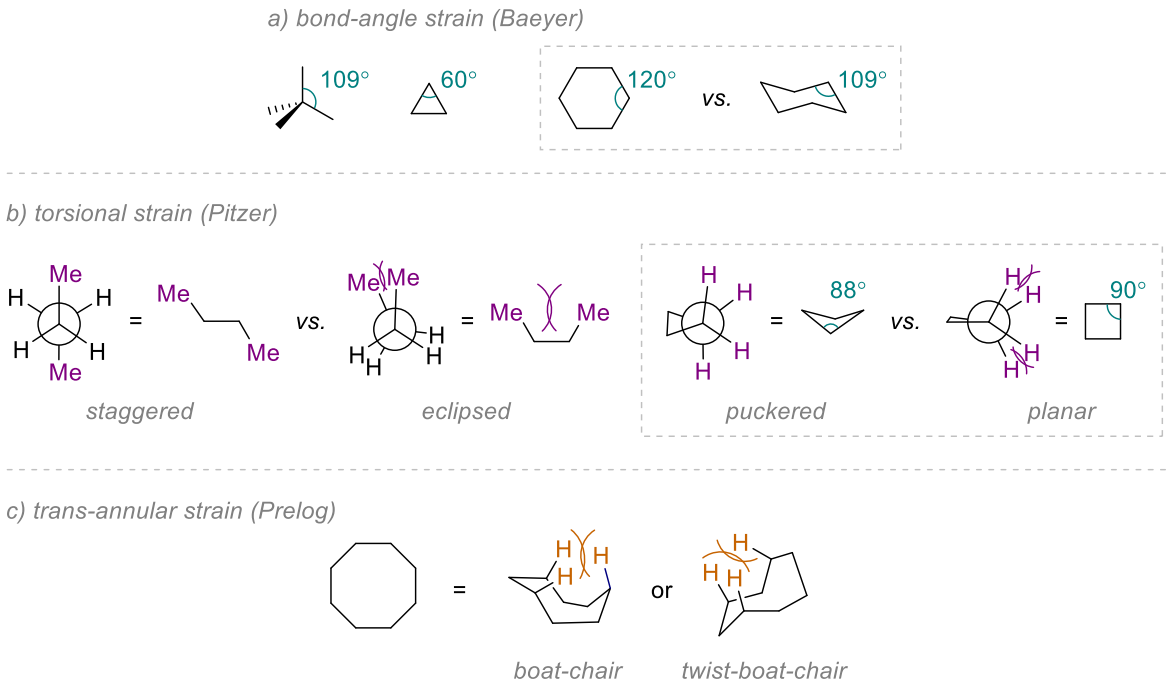


Figure 1. Elements of strain in cyclic molecules.

Torsional strain involves the steric repulsion of atoms 4 bonds apart. These interactions, along with hyperconjugative stabilisation effects, lead to antiperiplanar being the preferred conformation over other eclipsed or gauche conformations in a molecule such as butane (Figure 1b). The relief of torsional strain is the reason cyclobutane adopts the puckered butterfly geometry with staggered substituents over the planar square geometry with eclipsed substituents. The internal bond angles of the puckered geometry are in fact smaller, so the relief of torsional strain is at the expense of bond-angle strain.[2,3]

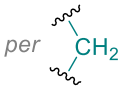
Trans-annular strain is also steric in nature and relates to the repulsion of substituents on non-adjacent atoms in a ring (Figure 1c).[4] Alicyclic molecules with larger rings experience trans-annular strain as most conformations bring groups on opposite sides of the ring within close proximity. Trans-annular strain is not present in small ring molecules such as cyclopropane and cyclobutane, however, the combination of high bond-angle strain and torsional strain means that these alicyclic compounds have greater internal energy, or strain energy (SE).[2]

1.1.3. Strain energy

Total ring strain is a combination of Baeyer, Pitzer and Prelog strain and can be determined by taking the heat of formation (ΔH_f) of the strained compound and subtracting ΔH_f of a strain-

free reference.[2] This calculated value is the defined strain energy (SE) and is a useful tool when considering how the thermodynamic stability of a molecule is affected by ring strain.

Table 1. The calculation of strain energy (SE) for cyclopropane using cyclohexane as the "strain-free" reference.

		per 	
ΔH_f /kcal mol^{-1}	−29.5	−4.9	12.7

$SE_{(cyclopropane)} = \Delta H_f$ – strain-free reference

$= 12.7 - 3(-4.9) = 27.4$ kcal mol^{-1}

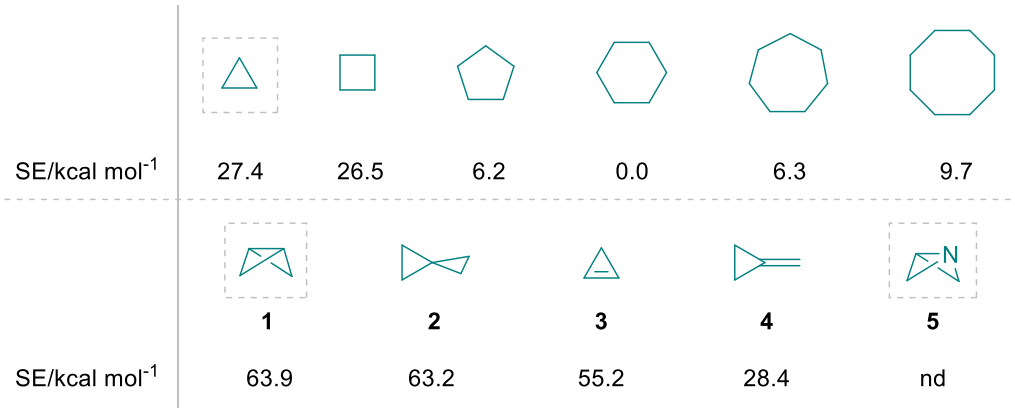
Relative to other cyclic molecules, cyclohexane is defined as having a strain energy of zero, as the internal bond angles are an optimal 109° and the substituents are all in a staggered orientation. By dividing the ΔH_f of cyclohexane by six, the value obtained is considered the ΔH_f of one strain-free methylene unit (Table 1). This value can be used to determine the strain-free reference for other cyclic molecules to calculate their strain energy. For example, the strain-free reference of cyclopropane is three of these methylene units. Taking the ΔH_f of cyclopropane and subtracting the reference determines the strain energy of cyclopropane to be 27.4 kcal mol^{-1} (Table 1).

As the calculation of strain energy requires the approximation of a strain-free reference, reported values can vary between studies. In addition, ΔH_f can be determined both experimentally and computationally using various techniques.[5] Nevertheless, strain energy is still useful to compare the relative thermodynamic stabilities of cyclic structures. SE values of selected cyclic molecules are reported in Table 2.[2] As cyclohexane is established as the strain-free reference, its strain energy is defined as 0 kcal mol^{-1}. From cyclohexane, there is a trend of increasing strain energy with decreasing ring size due to increased Baeyer and Pitzer strain. Moving to rings larger than cyclohexane is also accompanied by increasing strain energy due to greater Prelog strain. This trend continues up to cyclononane, after which the sufficiently large rings can adopt conformations with few trans-annular interactions.

Bicyclic small-ring molecules can have greater strain energy than the sum of the individual rings. For example, bicyclo[1.1.0]butane[6] (**1**) has an SE value of 63.9 kcal mol^{-1}, which is higher than the sum two cyclopropanes. This is because the two rings are not independent and serious distortion in bond angles at the bridgehead carbon are required to form the bicycle. A

similar effect is observed in spiro[2.2]pentane (**2**), which has a strain energy 8.4 kcal mol^{-1} higher than the sum of two cyclopropanes.[2]

Table 2. Reported strain energies of selected cyclic molecules.[2]



The introduction of unsaturation into rings increases the strain energy as the optimal angle of a trigonal planar sp^2 centre is 120°, which is severely distorted in molecules such as cyclopropene (**3**) and methylene cyclopropane (**4**).[2]

1.1.1. Cyclopropane

The strain energy of a molecule such as cyclopropane refers to a measure of relative thermodynamic stability, however with regards to reactivity, kinetic stability must be considered. In fact, strained molecules are also kinetically activated compared to unstrained molecules as structural deformation leads to a change or distortion in orbital hybridisation.

A simple model for the bonding of cyclopropane states that due to the extremely acute bond angles, the C–C bonds are "bent" and a significant proportion of electron density is located outside the internuclear axis (Figure 2a).[7] In addition, to maximise orbital overlap, the C–C bonds have more p-character and so are more olefinic than unstrained C–C bonds.[8] This change in hybridisation accounts for the difference in reactivity of cyclopropane compared to acyclic saturated alkanes. For example, cyclopropanes can stabilise α-carbocations better than other acyclic alkyl groups as the C–C σ-bonds with high p-character can donate into the adjacent empty p orbital of the carbocation (Figure 2b).[9]

Furthermore, the high p-character of the C–C bonds in cyclopropane is associated with high s-character in the C–H bonds of cyclopropane. The pKa of cyclopropane is therefore lower than expected, between that of ethylene and propane (Figure 2c).[10,11]

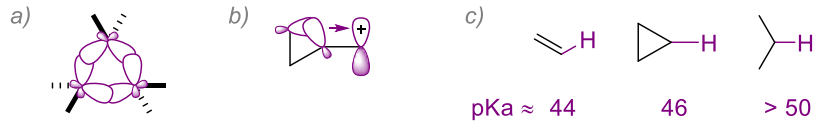


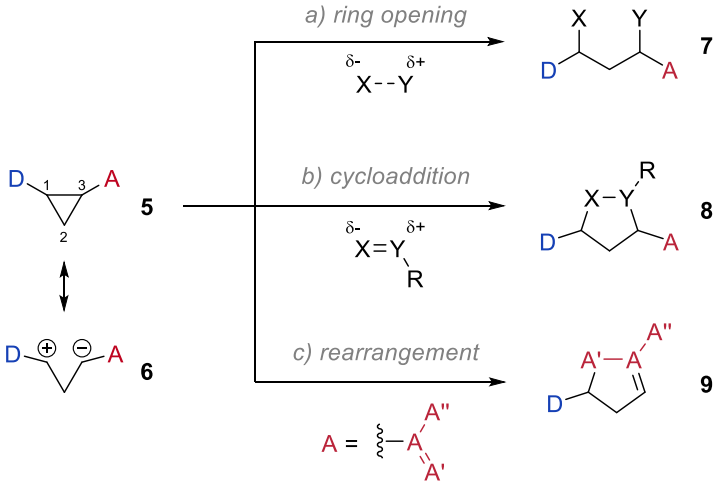
Figure 2. a) The "bent bond" model of cyclopropane. b) The stabilisation of an α-carbocation by cyclopropane. c) Approximate acidity of cyclopropane relative to ethylene and propane.

This thesis focuses on the reactivity of activated cyclopropanes and azabicyclo[1.1.0]butanes (**5**) with reference to some bicyclo[1.1.0]butanes. Therefore, a further introduction into these strained molecules is outlined below.

1.2. Selected strained molecular building blocks

1.2.1. Donor-acceptor cyclopropanes

While kinetically and thermodynamically activated with respect to acyclic saturated alkanes, cyclopropane is still a relatively inert motif, as forcing conditions such as transition metal oxidative insertion[12] are required for C–C bond cleavage. The kinetic activation of cyclopropanes with certain substituents enables more facile and selective C–C bond cleavage reactions. Specifically, the vicinal substitution of a cyclopropane with an electron-donating and electron-withdrawing group gives structures referred to as donor-acceptor cyclopropanes (DA cyclopropanes, **5**, Scheme 1).[13,14] Such species have broad strain-release reactivity arising from the polarisation of one of the cyclopropane C–C bonds. These reactions are summarised in Scheme 1, where D is an electron donating group, such as an electron rich aryl group, and A is an electron withdrawing group, such as a carbonyl functionality.

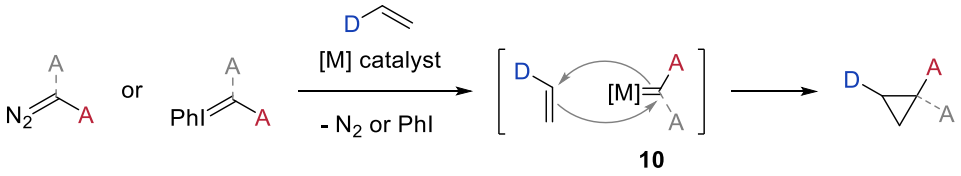


Scheme 1. General reactivity of donor-acceptor cyclopropanes.

DA cyclopropanes can be visualised as a tight zwitterionic species (**6**) where a build-up of positive charge at C1 is stabilised by the electron donating group, while a build-up of negative charge at C3 is stabilised by the electron withdrawing group. The chemistry of DA cyclopropanes is governed by polar reactions occurring at these two sites.

For example, nucleophilic addition to C1 or electrophilic addition to C2 is a common reaction profile of DA cyclopropanes, which leads to the selective formation of diversely substituted acyclic molecules (**7**, Scheme 1a). Similarly, dipolar cycloaddition reactions are possible to give ring expanded products (**8**, Scheme 1b), and DA cyclopropanes can rearrange, which leads to the formation of heterocycles (**9**, Scheme 1c).

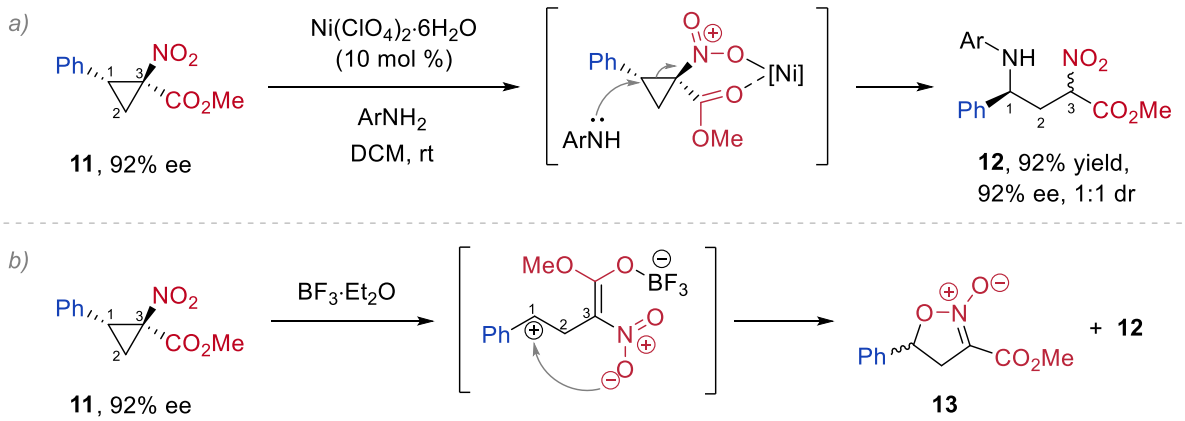
Reported syntheses of cyclopropanes often employ highly energetic species such as reactive carbenoid precursors. In the context of DA cyclopropanes, the most common reaction of this type is the addition of a transient metal carbene bearing an electron withdrawing group to an electron rich alkene (Scheme 2).



Scheme 2. Synthesis of donor-acceptor cyclopropanes.

The transient metal carbene (**10**) is formed by the decomposition of electron deficient diazo compounds or phenyliodonium ylides in the presence of a transition metal catalyst.[15,16] This intermediate reacts readily with electron rich alkenes to yield cyclopropanes bearing both an electron donating group and an electron withdrawing group. The most frequently employed metal catalysts for this transformation are rhodium or copper complexes. In addition, enantioselective variants with chiral rhodium or copper complexes have been developed to access enantioenriched DA cyclopropanes.[17,18]

Focussing on nucleophilic addition to DA cyclopropanes, the activation of the electron withdrawing group of a DA cyclopropane with a Lewis or Brønsted acid enables nucleophilic attack at C1 with concurrent C–C bond cleavage under exceptionally mild conditions.[19–24] Scheme 3a shows an example published by Charette and co-workers whereby the di-acceptor motif of DA cyclopropane **11** is activated by a nickel Lewis acid catalyst.[19] This promotes nucleophilic attack at the electrophilic carbon by aryl amines.



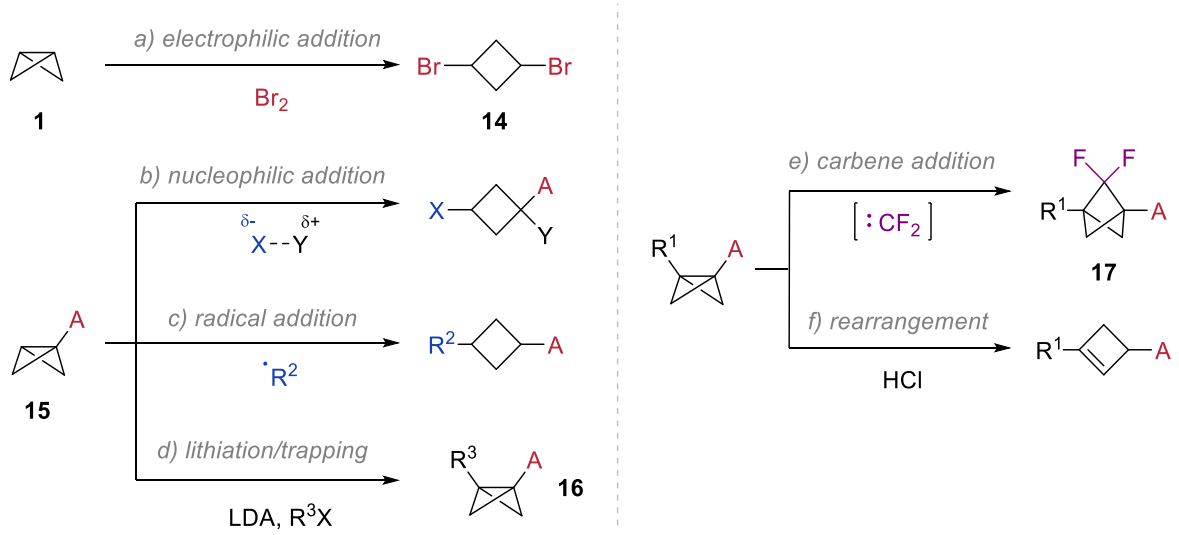
Scheme 3. a) Lewis acid catalysed nucleophilic addition of amines to donor-acceptor cyclopropanes. b) Intramolecular rearrangement side reaction with certain Lewis acids.

The authors observed that enantioenriched DA cyclopropanes underwent nucleophilic addition to give ring-opened products **12** with no loss of enantiomeric excess (ee) at C1. This is due to a stereospecific S_N2 mechanism, whereby the nucleophile attacks the cyclopropane C–C σ* antibonding orbital leading to an inversion of stereochemistry.[19] This chirality transfer mechanism is typical of DA cyclopropane chemistry and has been widely demonstrated as a useful tool in the synthesis of acylic molecules with sterodefined centres.[25]

However, Charette and co-workers also demonstrated that the choice of Lewis acid has a significant effect on the reaction outcome.[19] When strongly Lewis acidic, monodentate boron trifluoride etherate ($BF_3.Et_2O$) was employed as a catalyst, the formation of racemic intramolecular rearrangement product **13** was observed alongside the desired product (Scheme 3b). This is due to the formation of a full carbocation at C1 and enolate at C2, rather than a configurationally stable zwitterionic intermediate. The nucleophilic oxygen can then attack either side of the planar C1 carbocation leading to racemate **13**.[19] This example demonstrates the importance of balance between reactivity and selectivity in the chemistry of DA cyclopropanes that enables the synthesis of enantioenriched ring-opened products.

1.2.2. Bicyclo[1.1.0]butane

The kinetic activation of cyclopropane is also made possible by its incorporation into a bicycle. Bicyclo[1.1.0]butane, or BCB (**1**, Scheme 4), is comprised of two cyclopropane rings that share a bridging C–C bond.[6] The bridge bond is so strained that the bonding orbital is highly distorted with considerable p character for a formal σ-bond. The consequence is that the bridge bond reacts in a similar way to a C=C π bond, for example, BCB reacts readily with bromine to give 1,3-dibromocyclobutane (**14**, Scheme 4a).[6,26]



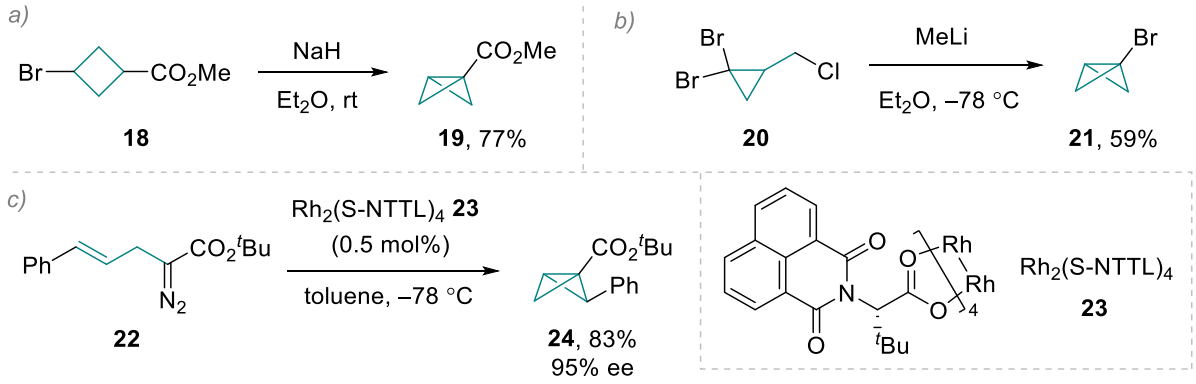
Scheme 4. General reactivity of bicyclo[1.1.0]butanes.

The reactivity of BCBs bearing an electron withdrawing group (**15**) mirrors that of electron deficient alkenes as they can act as Michael acceptors in nucleophilic addition reactions (Scheme 4b).[27–31] Furthermore, the addition of nucleophilic radicals has been reported, whereby the BCB resembles a Giese acceptor (Scheme 4c).[32,33] Both such strain-release reactions lead to the selective formation of functionalised cyclobutanes, which are a privileged class of molecular scaffold.

Another reactivity mode of electron deficient BCBs is their deprotonation at the bridgehead position. Due to the highly strained bridging C–C bond, the bridgehead C–H bond with its high degree of s character can be easily deprotonated with LDA.[27,34] Subsequent electrophilic trapping gives 1,3-disubstituted BCBs (**16**, Scheme 4d). The use of BCBs to access other valuable strained building blocks has also been demonstrated, for example, the reaction of 1,3-disubstituted BCBs with difluorocarbene to give bicyclo[1.1.1]pentane derivatives **17** (Scheme 4e).[35,36] Furthermore, the rearrangement of BCBs to give cyclobutenes is well documented and noted as a common reaction pathway of BCBs (Scheme 4f).[27,30,37]

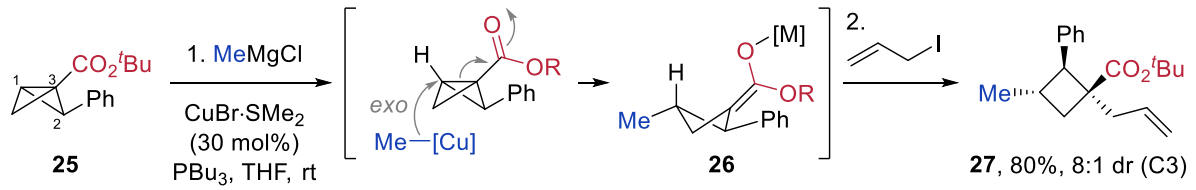
The first high yielding synthesis of a BCB derivative was performed by Wiberg and co-workers and involved the base mediated cyclisation of 3-bromocyclobutane-1-carboxylate **18** to give BCB ester **19** (Scheme 5a).[6] As cyclobutanes are themselves difficult to prepare, modern approaches to BCBs often utilise cyclopropanes as precursors. For example, BCB bromide (**21**) is easily accessible from dibromo cyclopropane **20** *via* lithium-bromine exchange with methyllithium followed by intramolecular cyclisation (Scheme 5b).[38] Alternatively, the construction of both rings of BCB in one transformation is possible from diazo ester **22**.[39] An

enantioselective intramolecular cyclopropanation of **22**, catalysed by dirhodium complex **23**, afforded BCB **24** in 95% enantiomeric excess (ee).



Scheme 5. Selected synthetic routes to bicyclo[1.1.0]butanes.

A specific example of nucleophilic addition to an electron deficient BCB is shown in Scheme 6.[39] Here, Fox and co-workers reported a copper catalysed nucleophilic addition of methyl magnesium chloride to electron deficient BCB **25**. The S_N2-like nucleophilic addition of the *in situ* formed cuprate to C3 occurs selectively on the exo face to give enolate **26**. The enolate is then quenched by the addition of allyl iodide to give highly substituted cyclobutane product **27**. The electrophile addition occurs preferentially from the less hindered face affording the product in an 8:1 diastereomeric ratio (dr).



Scheme 6. Nucleophilic addition to an electron deficient bicyclo[1.1.0]butane.

1.2.3. Azabicyclo[1.1.0]butane

An interesting analogue of bicyclo[1.1.0]butane is azabicyclo[1.1.0]butane, or ABB (**5**, Figure 3), where one bridgehead C–H unit is replaced by a nitrogen atom.[40] While under-investigated with respect to BCB,[41] ABB-containing molecules have attracted significant recent attention due to their strain-release reactions that yield azetidines, which are valuable synthetic targets in medicinal chemistry.[42–47]

The strain energy of ABB has not been reported to date, however, the strained structure resembles that of BCB. Comparing the structures of triphenyl ABB **28** and dicyano BCB **29**, both determined by single crystal X-ray diffraction,[48,49] the bridge bond lengths are similar at

1.52 Å and 1.50 Å respectively. Furthermore, the dihedral angles of the intersecting planes of the two 3-membered rings for **28** and **29** have been determined as 119° and 126° respectively.

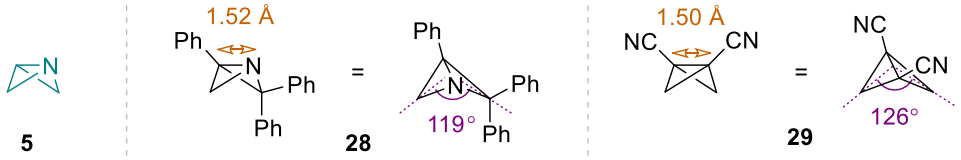
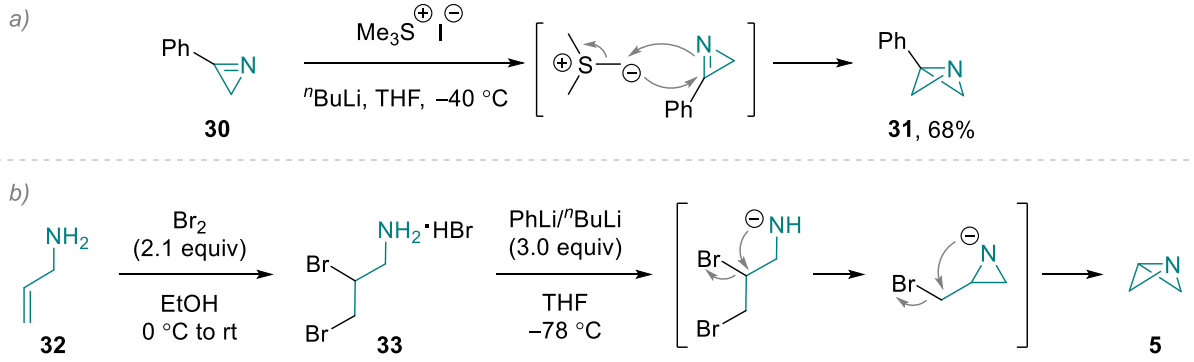


Figure 3. Structure of azabicyclo[1.1.0]butane and similarity to bicyclo[1.1.0]butane.

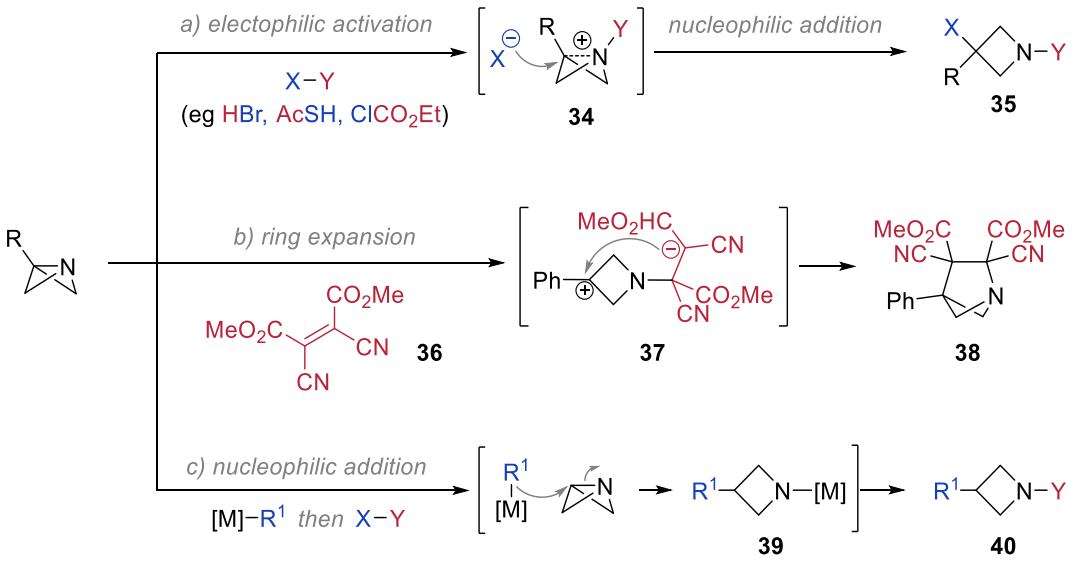
The first synthesis of an azabicyclo[1.1.0]butane derivative (**31**) was reported by Hortmann and co-workers in 1972, which involved the aziridination of azirine **30** with sulfonium methylide (Scheme 7a).[50] An efficient synthesis of the parent unsubstituted ABB (**5**) was established by Nagao and co-workers in 1999, which proceeds in only two steps from allyl amine **32** (Scheme 7b).[51] The first step is the dibromination of allyl amine to give ammonium salt **33**; the addition of 3 equivalents of strong base then leads to the formation of ABB *via* two consecutive intramolecular cyclisation reactions.



Scheme 7. Selected synthetic routes to azabicyclo[1.1.0]butanes.

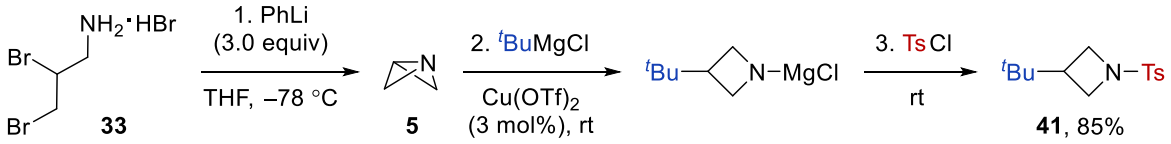
ABB has a heteroatom with a lone pair of electrons that can be readily activated with reagents such as hydrogen bromide (Scheme 8a).[51] The nitrogen is first protonated to give strained ammonium **34**, which is extremely electrophilic and reacts with strain-release by the nucleophilic addition of the counteranion to give 1,3-azetidine **35**. The equivalent reaction also occurs with electrophiles such as thioacetic acid and ethyl chloroformate.[51,52]

The ABB nitrogen lone pair can also interact with electron deficient alkenes such as **36** (Scheme 8b).[53] This leads to the formation of zwitterion **37** that undergoes intramolecular ring closure to give ring-expanded azabicycle **38**.



Scheme 8. General reactivity of azabicyclo[1.1.0]butanes.

ABB has also been shown to undergo direct nucleophilic addition at the bridgehead carbon by strong nucleophiles (Scheme 8c).[28,54] This gives metalated azetidine **39** that can undergo a subsequent reaction at nitrogen to give 1,3-substituted azetidine product **40**. An example of one such reaction is shown in Scheme 9. In a one-pot procedure, ABB is first generated from ammonium salt **33** by the addition of phenyllithium. The addition of *tert*-butyl magnesium chloride in the presence of a copper catalyst results in the strain-release alkylation of ABB. Finally, the addition of *p*-toluenesulfonyl chloride (TsCl) leads to the formation of alkylated azetidine **41** in 85% yield.[54]

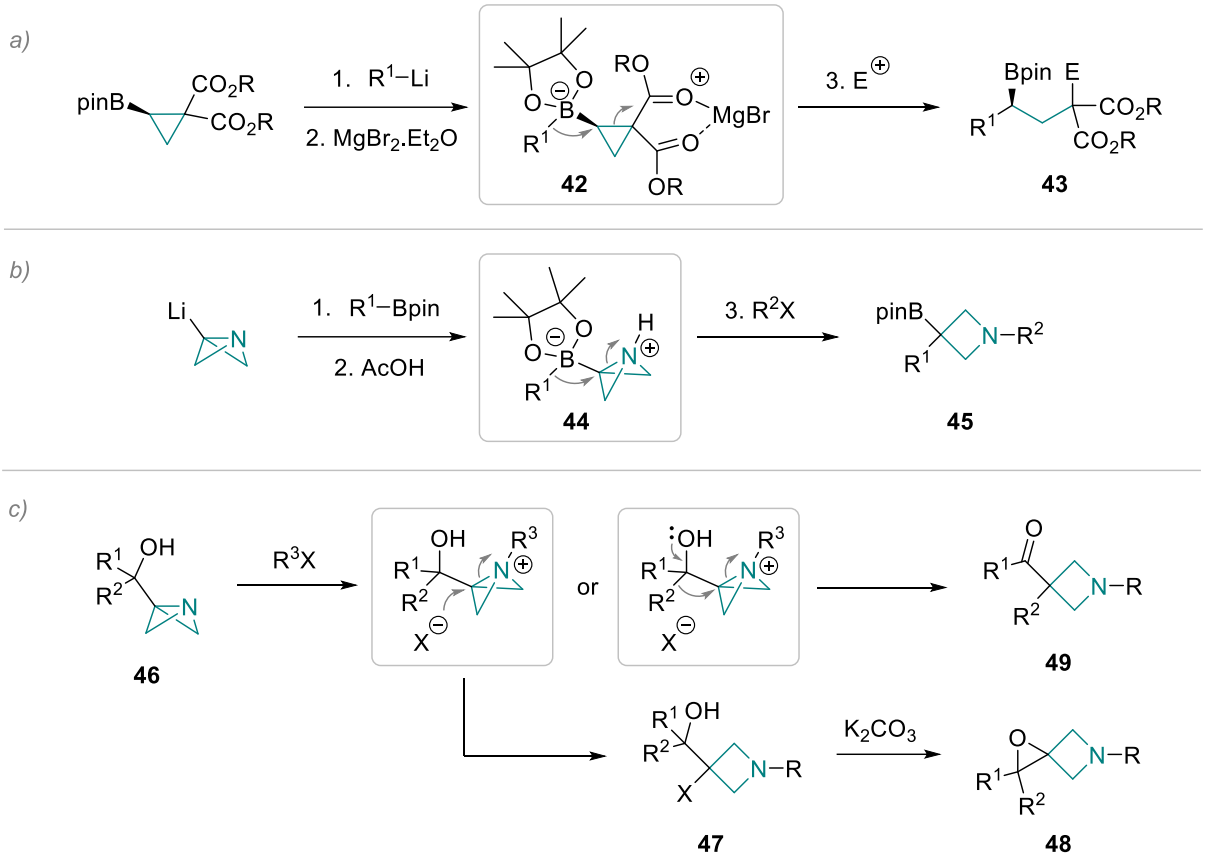


Scheme 9. Direct nucleophilic alkylation of azabicyclo[1.1.0]butane.

1.3. Outline of projects

The investigation of new strain-release driven transformations of the strained building blocks introduced above was undertaken. This was done with the aim of establishing efficient, modular routes to diversely decorated molecules with interesting molecular scaffolds.

Chapter 2 discusses the strain-release C–C bond cleavage of a novel class of DA cyclopropane where the donor group is a tetrahedral boronate complex (**42**, Scheme 10a). Such species undergo a 1,2-metallate rearrangement upon activation of the DA cyclopropane with a Lewis acid. This protocol provides access to enantioenriched γ-carbonyl boronic esters **43**.



Scheme 10. Outline of the strain-release transformations discussed in chapters 2, 3 and 4.

A similar reaction mechanism operates in the transformation discussed in Chapter 3, where the 1,2-metallate rearrangement of azabicyclo[1.1.0]butyl boronate complexes **44** is investigated (Scheme 10b). This reaction leads to the formation of 1,3,3-substituted azetidines **45**. The applicability of this reaction was demonstrated by the short synthesis of cobimetinib, an anti-cancer pharmaceutical drug containing the azetidine motif.

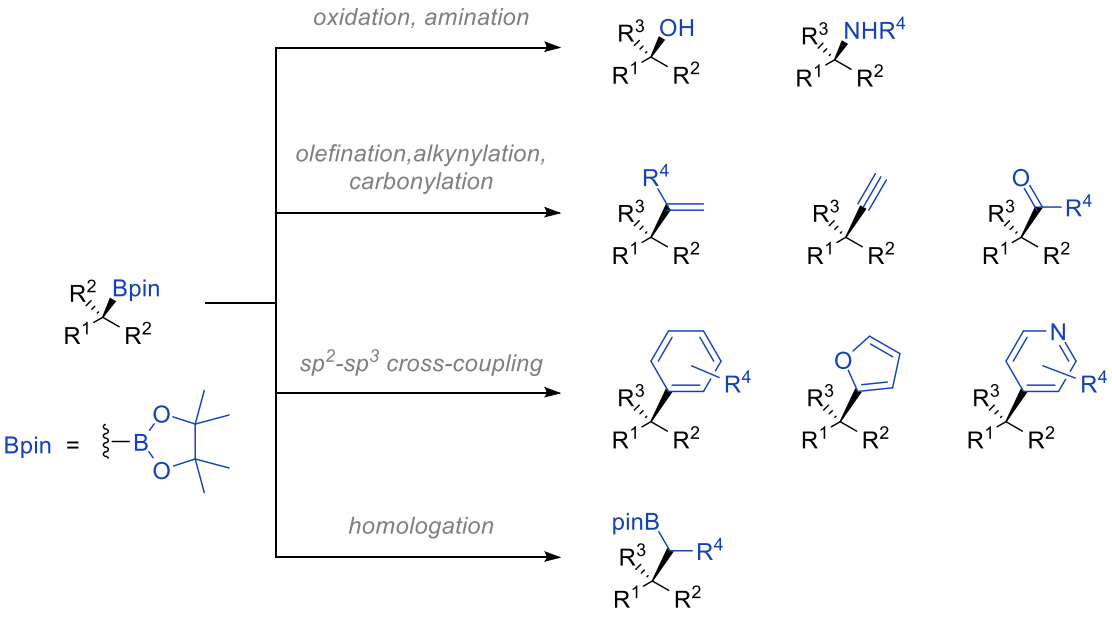
Chapter 4 discusses the divergent strain-release reactivity of azabicyclo[1.1.0]butyl carbinols (**46**, Scheme 10c). Upon the addition of an activating agent, activation of ABB followed by nucleophilic addition of the counter anion to the bridgehead position occurs to give halohydrin **47**, which can be easily converted to spiroepoxy azetidine **48**. Alternatively, a semipinacol rearrangement proceeds to give keto azetidine **49**. The semipinacol rearrangement is reminiscent of the 1,2-metallate rearrangement developed in chapter 3.

2. Strain-release of donor-acceptor cyclopropyl boronate complexes

2.1. Introduction to boronic esters

2.1.1. Boronic esters in organic synthesis

Building block approaches to organic synthesis require molecular fragments that can be efficiently assembled through the formation of C–C or C–X bonds. Boronic esters serve as stable but versatile functional groups used as precursors for these key cross-coupling steps in a synthetic route. One such reaction that employs the boronic ester functional group is the Suzuki-Miyaura reaction.[55] Since the first publication by A. Suzuki in 1979,[56] the reaction has been developed extensively and is now the most popular palladium catalysed cross-coupling reaction used in the pharmaceutical industry.[57] An advantage of this process is that organoboron reagents are cheap and accessible, while boron containing by-products generally have low toxicity and are easy to remove.[57]



Scheme 11. Selected stereospecific transformations of alkyl boronic esters.

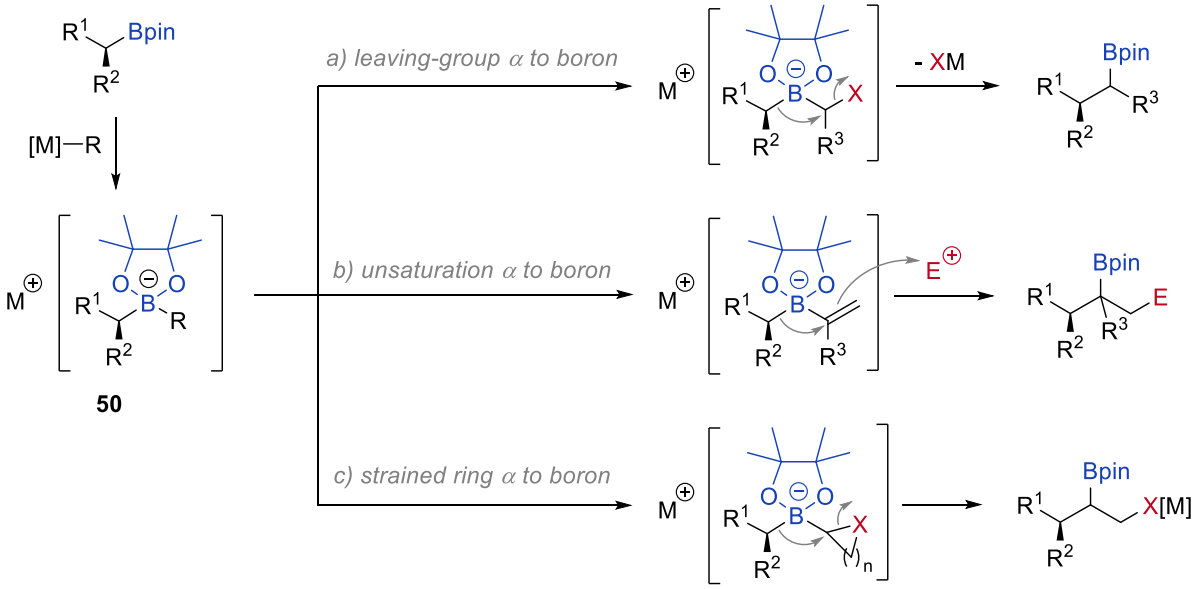
Since the discovery and development of the Suzuki-Miyaura reaction, the unique balance between reactivity and stability of boronic esters, particularly pinacol boronic esters, has enabled the development of a host of C–C or C–X bond forming reactions from these versatile reagents. Many recent advances in this field involve enantiospecific transformations of readily available enantioenriched alkyl boronic esters to give molecules with tailored 3-dimensional

shapes (Scheme 11).[58,59] These reactions often employ the enantiospecific 1,2-metallate rearrangement mechanism of boronate complexes.

2.1.2. 1,2-Metallate rearrangement of boronate complexes

While more stable to chromatography than unhindered boronic esters or boranes, pinacol boronic esters still possess a vacant p orbital centred on boron that can be readily attacked by nucleophiles. This results in the formation of a tetrahedral boronate complex with a formal negative charge (**50**, Scheme 12). If the carbon atom α to boron in a boronate complex is suitably electrophilic, a 1,2-metallate rearrangement can occur, whereby one substituent on boron migrates to give a homologated boronic ester. This mechanism leads to the formation of a new C–C or C–X bond with a retained boronic ester functional group.

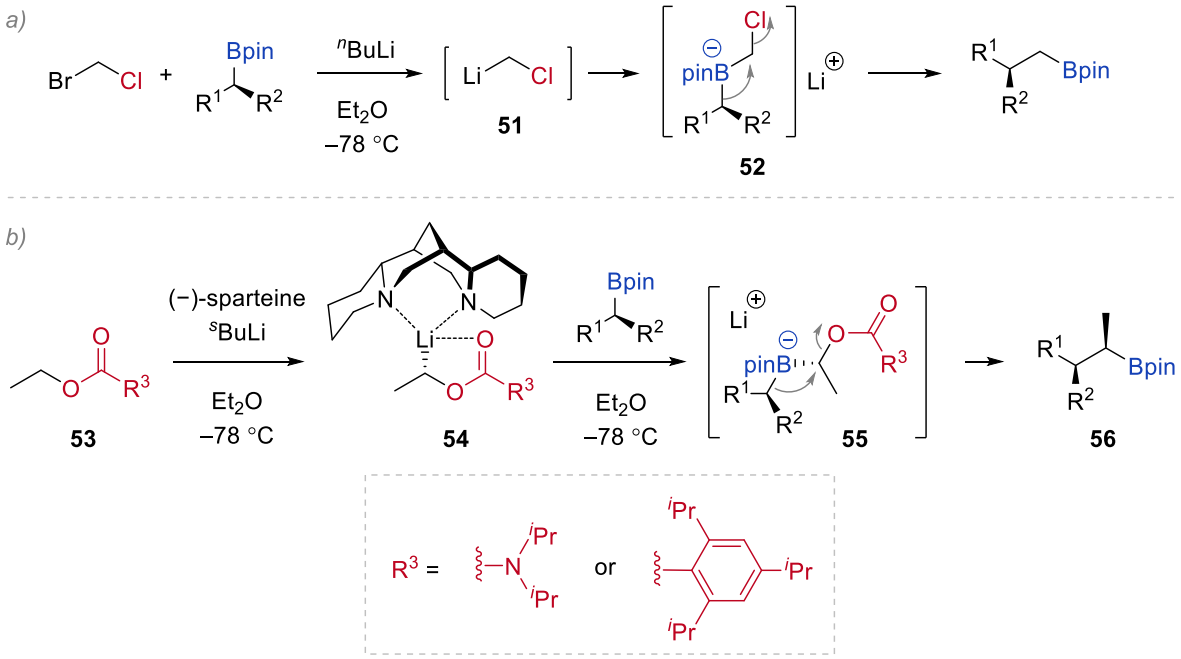
The 1,2-metallate rearrangement can be triggered by the loss of a leaving group α to boron (Scheme 12a). Alternatively, a boronate complex with unsaturation α to boron can be activated by the addition of an electrophile that induces the 1,2-shift (Scheme 12b). Overall, this reaction constitutes a 3-component coupling reaction. Finally, the use of a strained organometallic species leads to the formation of a boronate complex with a strained ring α to boron, which can undergo a strain-release-driven 1,2-metallate rearrangement reaction (Scheme 12c).



Scheme 12. Boronate complex formation and methods for triggering a 1,2-metallate rearrangement mechanism.

2.1.3. Leaving-group-driven 1,2-metallate rearrangement of boronate complexes

The Matteson homologation reaction is one example of a leaving-group-driven 1,2-metallate rearrangement (Scheme 13a).[60] The lithium-halogen exchange of bromochloromethane gives lithium carbenoid **51** that, in the presence of a boronic ester, undergoes borylation to form boronate complex **52**. Subsequently, chloride in the α position acts as a leaving group to facilitate a 1,2-metallate rearrangement. For this to occur, the migrating alkyl group and the leaving group require an antiperiplanar arrangement for electron density to be donated into the C–Cl σ* antibonding orbital. This means that when enantioenriched boronic esters undergo this transformation, the products are produced with complete enantiospecificity.[58] Significantly, this reaction has the advantage of the conservation of the boronic ester functional group in the product, which serves as a useful functional handle for further chemical manipulations.[58]

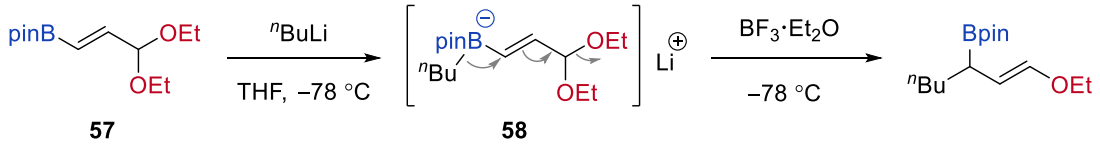


Scheme 13. 1,2-Metallate rearrangement of boronate complexes with α leaving groups.

An extension to the Matteson homologation reaction is the use of sterically hindered carbamate or benzoate esters as leaving groups. This is generally referred to as lithiation–borylation methodology (Scheme 13b).[61–63] The advantage of this system is that configurationally stable lithiated carbenoids, such as **54**, can be accessed in high ee by (−)-sparteine-mediated lithiation of starting material **53**.[64] The addition of a chiral boronic ester to **54** leads to the formation of

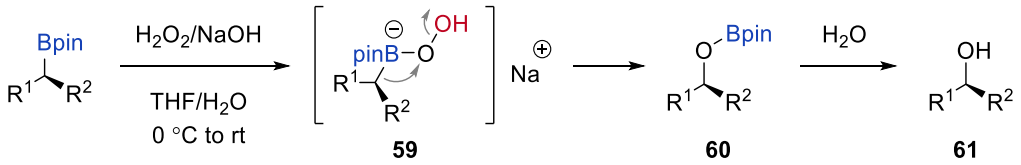
boronate complex **55**. Subsequent enantiospecific 1,2-metallate rearrangement leads to homologated products such as **56**, which contains two contiguous stereocentres.

Vinylogous Matteson homologation reactions have also been reported (Scheme 14).[65,66] Here, the leaving group is positioned in the γ position of vinyl boronate complex **58**, which is formed by the addition of *n*-butyllithium to vinyl boronic ester **57**. The 1,2-metallate rearrangement occurs through conjugation, driven by the loss of the leaving group upon activation with a Lewis acid.



Scheme 14. Vinylogous Matteson homologation; 1,2-metallate rearrangement with conjugated γ leaving groups.

The oxidation of boronic esters with basic hydrogen peroxide also involves an enantiospecific 1,2-metallate rearrangement mechanism (Scheme 15).[58] The mixture of hydrogen peroxide and sodium hydroxide leads to the formation of hydroperoxyl anions that react with boronic esters to form boronate complex **59**. A 1,2-metallate rearrangement then occurs, driven by the loss of the hydroxyl leaving group, to give borate **60** followed by alcohol **61** upon hydrolysis.

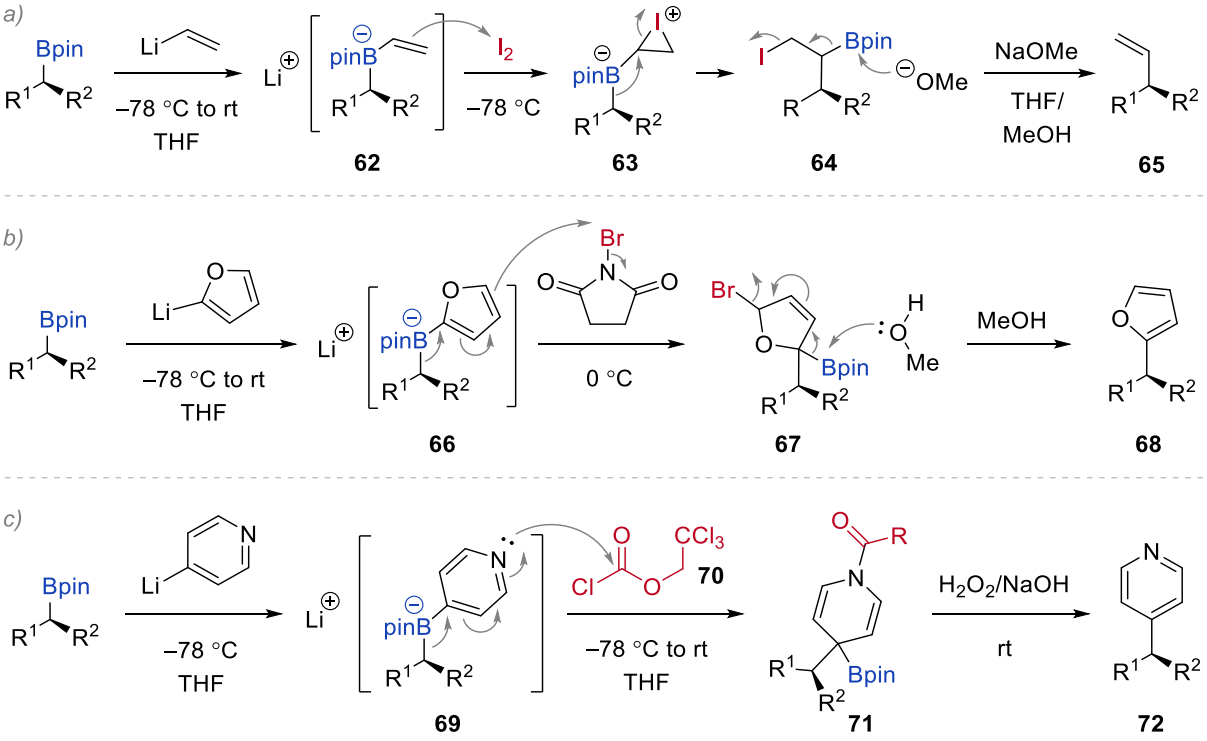


Scheme 15. Enantiospecific oxidation of boronic esters.

2.1.4. 1,2-Metallate rearrangement of boronate complexes with unsaturation α to boron

Boronate complexes with unsaturation α to boron are generally nucleophilic and thus react with electrophiles through a 1,2-metallate rearrangement mechanism. The primary example of this is the Zweifel olefination reaction that stereospecifically transforms a boronic ester into an alkene (Scheme 16a).[67–69] Here, the addition of vinyllithium to an alkyl boronic ester leads to the formation of vinyl boronate complex **62**. The double bond of **62** reacts with iodine to form iodonium ion **63** that undergoes a 1,2-metallate rearrangement with alkyl migration to give β-iodo boronic ester **64**. Base-induced elimination leads to the formation of alkene product **65**.

A similar mechanism has been successfully applied to the sp^2-sp^3 coupling of aliphatic boronic esters with electron rich aromatics such as furan (Scheme 16b).[70,71] The addition of furan-2-yllithium to a boronic ester gives boronate complex **66** that undergoes a 1,2-metallate rearrangement upon the addition of electrophilic *N*-bromosuccinimide (NBS). Boronic ester **67** then eliminates, with the loss of bromide, to give rearomatised coupled product **68**.[70]

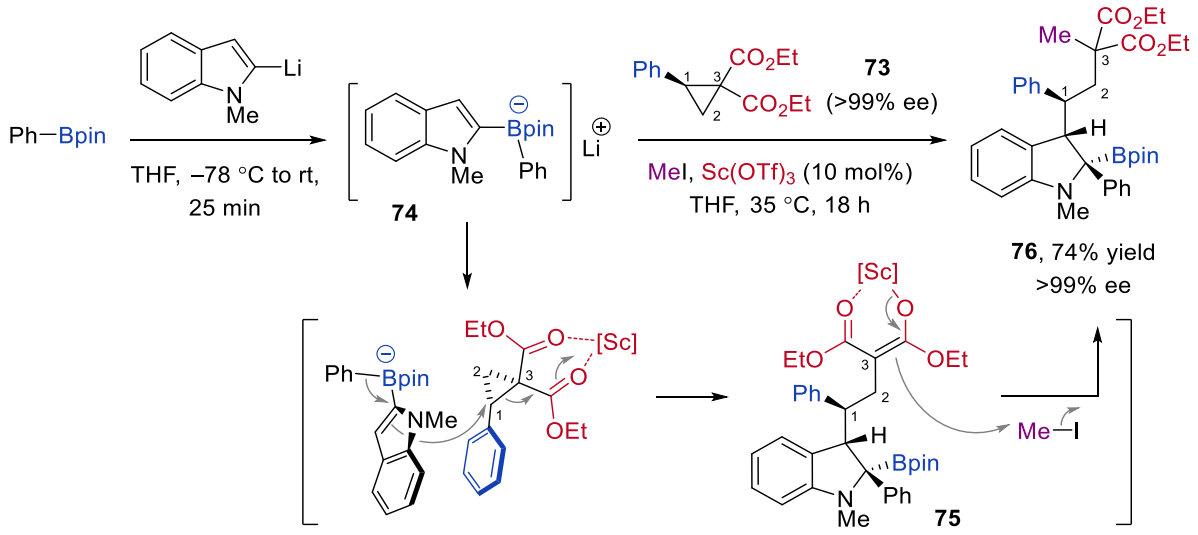


Scheme 16. Sp^2-sp^3 coupling of boronic esters and sp^2 organolithiums through electrophilic activation of the π system of the boronate complex.

Other sp^2-sp^3 couplings of this kind have been developed with the activation procedure chosen to target the specific aromatic coupling partner.[72–75] Another example is the coupling of a boronic ester to pyridin-4-yllithium (Scheme 16c).[72] Boronate complex **69** was activated by acylation of the pyridine nitrogen upon the addition of 2,2,2-trichloroethoxycarbonyl chloride (TrocCl, **70**). This leads to the stereospecific formation of dearomatised intermediate **71** after a 1,2-metallate rearrangement. Oxidation of the boronic ester with hydrogen peroxide/sodium hydroxide triggers an elimination to give coupled product **72** with a driving force of rearomatisation.

More recently, Studer and co-workers reported the nucleophilic addition of an indolyl boronate complex to a donor-acceptor cyclopropane (Scheme 17).[76] This is the first example of a

transformation that combines the reactivity of DA cyclopropanes and the 1,2-metallate rearrangement of boronate complexes.



Scheme 17. Dearomative nucleophilic addition of an indolyl boronate complex to a donor–acceptor cyclopropane.

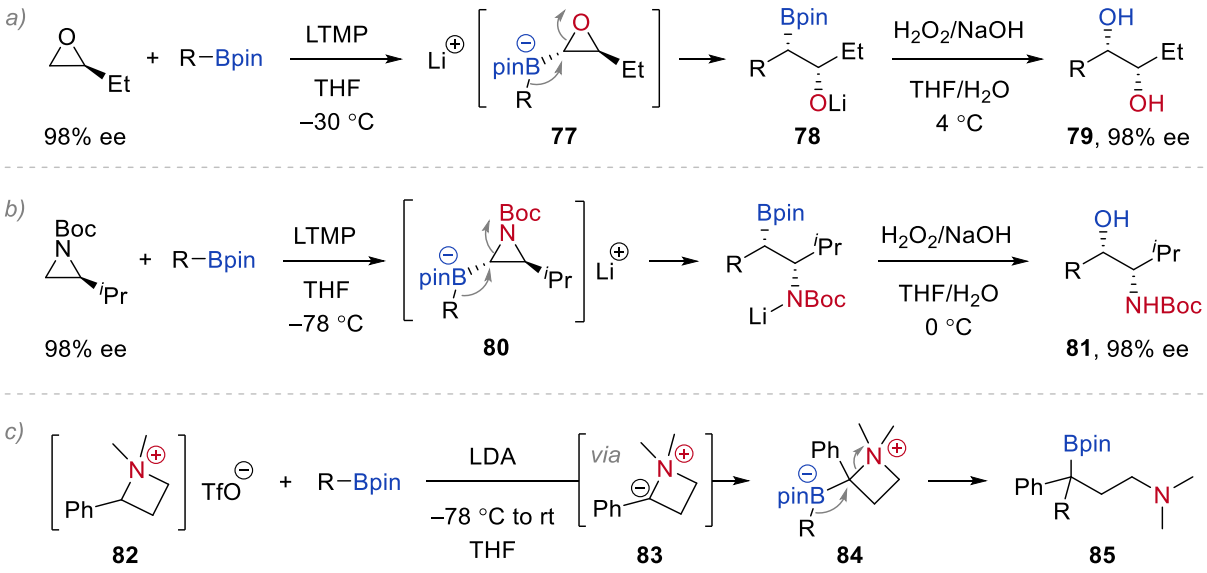
Enantioenriched diester substituted cyclopropane **73** is activated through coordination to a Lewis acid. Nucleophilic indolyl boronate complex **74** then undergoes a 1,2-metallate rearrangement with nucleophilic addition to the electrophilic C1 atom of the cyclopropane. Resulting enolate **75** is then trapped *in situ* by methyl iodide which liberates the Lewis acid catalyst. Coupled product **76** was obtained as a single diastereomer with inversion of stereochemistry at C1.[76]

2.1.5. 1,2-Metallate rearrangement of boronate complexes with a ring α to boron

While the Zweifel olefination reaction does involve the activation of a boronate complex with unsaturation α to boron, the key 1,2-metallate rearrangement step is triggered by the cleavage of a three-membered iodonium ring (**63**, Scheme 16a). The cleavage of a strained ring α to boron is another type of driving force that has been explored to trigger the 1,2-metallate rearrangement of boronate complexes.

In this manner, the homologation of boronic esters with enantioenriched lithiated epoxides has been reported (Scheme 18a).[77] Diastereoselective lithiation of (+)-epoxybutane is achieved by the addition of lithium tetramethylpiperidide (LTMP), and in the presence of a boronic ester, leads to the formation of boronate complex **77**. This species undergoes a strain-release

1,2-metallate rearrangement to give alkoxide **78**. To avoid elimination of the boronic ester, this species was oxidised *in situ* to give diol product **79** with high diastereoselectivity.



Scheme 18. 1,2-Metallate rearrangement driven by the cleavage of strained saturated heterocycles.

Aziridinyl boronate complex **80**, formed under similar conditions to **77**, has also been reported to undergo a 1,2-metallate rearrangement/ring opening reaction. This protocol affords enantioenriched β-amino alcohols **81** after boronic ester oxidation (Scheme 18b).[78]

Furthermore, the α-lithiation of azetidinium **82** by lithium diisopropylamide (LDA), in the presence of a boronic ester leads to the formation of azetidinium boronate complex **84**. This species was shown to undergo spontaneous ring opening to give γ-dimethylamino tertiary boronic ester **85** (Scheme 18c).[79] However, attempts to access **85** enantioselectively by the lithiation of an enantioenriched sample of **82**, were unsuccessful. It was reasoned that intermediate ylide **83** is configurationally unstable and so borylation can occur from either face to give racemic products.

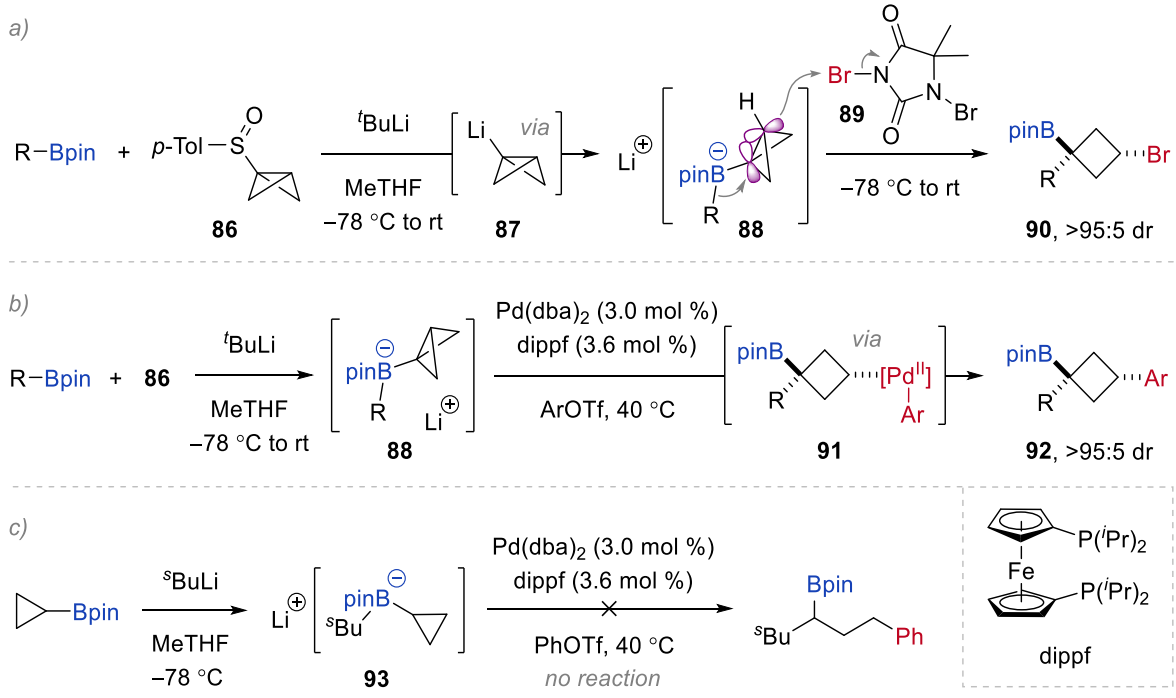
These three examples are efficient approaches to a C–C bond forming reaction. Here, the strained heterocycle not only induces the 1,2-metallate rearrangement but also introduces valuable functionality into the sp^3-sp^3 coupled products, in the form of hydroxy or amino groups.

To expand on this concept, it was reasoned that a 1,2-metallate rearrangement could be an efficient method to homologate boronic esters with carbocylic motifs. The driving force for such a transformation is the cleavage of the highly strained bridging C–C bond of BCB. This proposal was realised by employing BCB-sulfoxide **86** as a bench-stable source of BCB-

lithium (BCB-Li, **87**, Scheme 19a).[80,81] When a mixture of **86** and a boronic ester is treated with *tert*-butyllithium, rapid lithium-sulfoxide exchange occurs to generate BCB-Li that undergoes borylation to form strained boronate complex **88**. This species has been shown to react with electrophiles through a 1,2-metallate rearrangement – reminiscent of the reactivity of vinyl boronate complexes. For example, **88** reacts with brominating agent **89** to give cyclobutyl boronic ester **90**. Due to the high p-character of the bridge bond of **88**, a lobe of the bridge bond HOMO occupies the exo face of the bicycle so, to avoid steric interactions, the addition of the electrophile occurs stereoselectively on the same face as the migrating group.[80]

The use of palladium complexes as electrophiles has also been demonstrated (Scheme 19b).[81] Here, BCB-boronate complex **88** was reacted with aryl triflates in the presence of a palladium catalyst. Oxidative addition of the aryl triflate gives an electrophilic palladium-(II) species that reacts with **88** stereoselectively to give cyclobutyl palladium complex **91**. This undergoes reductive elimination to regenerate the active palladium catalyst and yield cross-coupled cyclobutyl boronic ester **92**.

Cyclopropyl boronate complex **93** was subjected to the same reaction conditions but did not undergo the 1,2-metallate rearrangement/ring opening mechanism (Scheme 19c).[81] This is significant as unlike BCB-boronate **88** and the heterocyclic examples shown in Scheme 18, **93** is not activated enough to trigger the 1,2-metallate rearrangement.

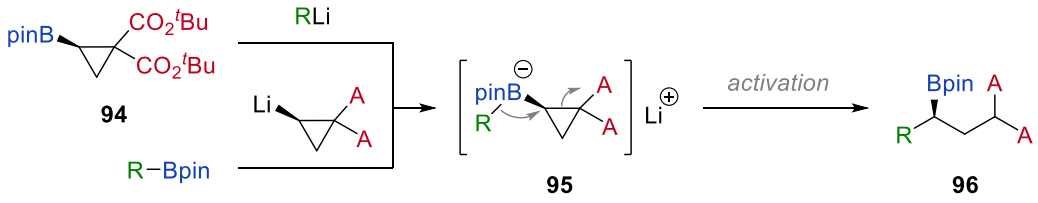


Scheme 19. 1,2-Metallate rearrangement driven by the cleavage of a strained C–C bond.

2.2. Project proposal

2.2.1. Project outline

This project looked to investigate the reactivity of cyclopropyl boronate complex **95,** which resembles a DA cyclopropane, where the donor group is the electron rich boronate and the acceptor groups are esters (Scheme 20).



Scheme 20. Reaction design for the 1,2-metallate/ring opening of cyclopropyl boronate complexes.

It was reasoned that boronate complex **95** could be accessed either by addition of an organolithium reagent to a cyclopropyl boronic ester, such as **94**, or by the addition of a lithiated cyclopropane to a boronic ester. A 1,2-metallate rearrangement of **95** would result in the formation of a new C–C bond at the expense of a strained cyclopropane bond. The product of such a reaction would be **96**, a secondary γ-carbonyl boronic ester. The use of either an enantioenriched sample of **94** or an enantioenriched configurationally stable lithiated cyclopropane would give enantioenriched products. This is because the 1,2-metallate rearrangement mechanism is enantiospecific and if **95** is configurationally stable, the mechanism would resemble the nucleophilic addition to DA cyclopropanes that proceeds through an enantiospecific S_N2 pathway.

The investigation into the proposed reaction summarised in this chapter is also outlined in the following publication: C. H. U. Gregson, V. Ganesh, V. K. Aggarwal, *Org. Lett.*, **2019**, *21*, 3412–3416.[82]

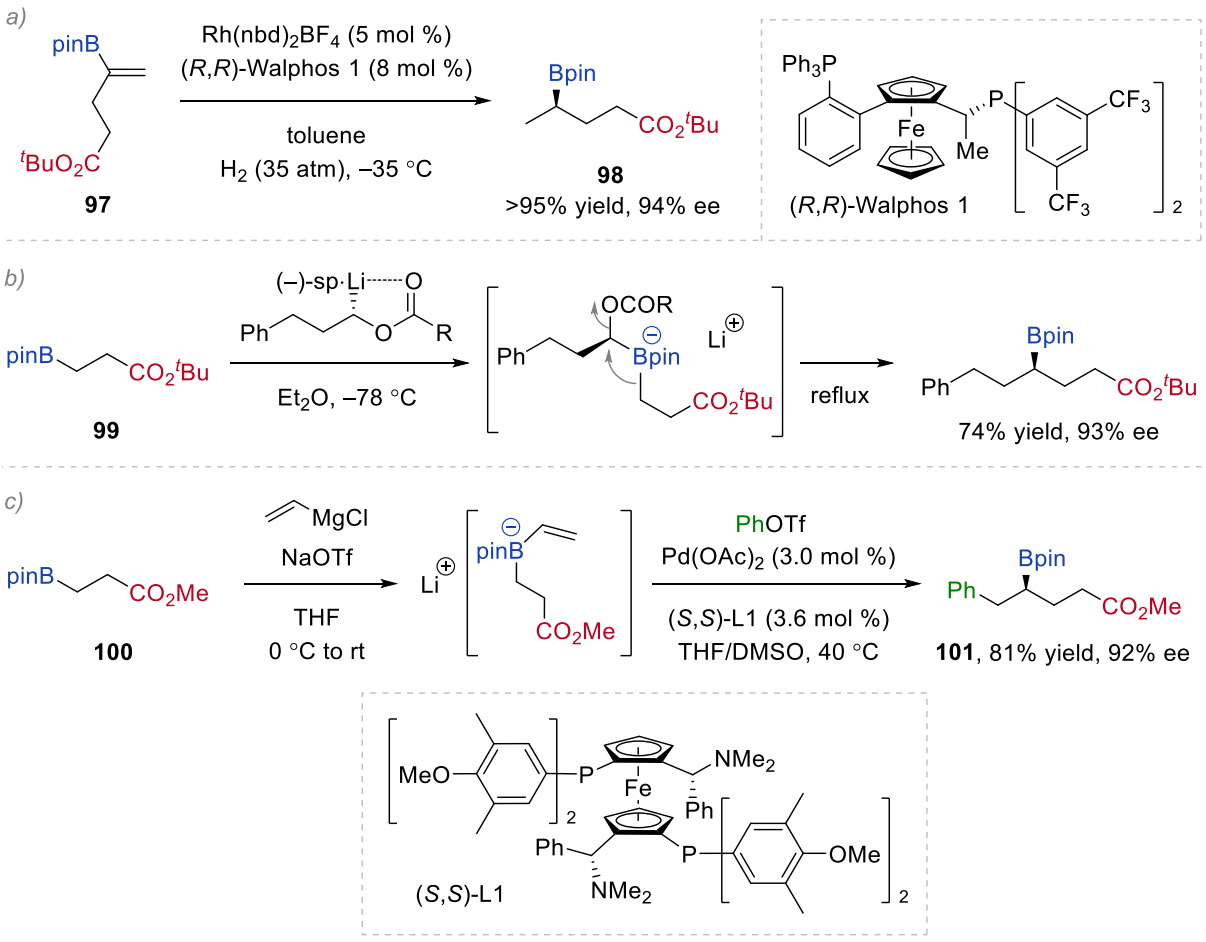
2.2.2. γ-Carbonyl boronic esters

Enantioenriched carbonyl boronic esters are an attractive chemical target as both the boronic ester and the carbonyl group are powerful functional handles for further chemical manipulations. However, there are few reports of the preparation of such building blocks with the boronic ester positioned γ to the carbonyl group in high enantiomeric excess.

One example is the rhodium catalysed hydrogenation of vinyl boronic ester **97** to give γ-carbonyl boronic ester **98** (Scheme 21a).[83] While this method does give products with high

ee, there is no concurrent functionalisation. On the other hand, similar products can be obtained using lithiation–borylation methodology (outlined previously in Scheme 13b), whereby β-carbonyl boronic ester **99** is homologated with a lithiated benzoate ester (Scheme 21b).[84] This method introduces a new carbon-carbon bond with good enantioselectivity but relies on the use of stoichiometric (−)-sparteine for enantioinduction.

Morken and co-workers developed alternative methodology which utilises a conjunctive cross-coupling mechanism to afford enantioenriched γ-carbonyl boronic esters from vinyl boronate complexes (Scheme 21c).[85] Here, β-carbonyl boronic ester **100** is transformed into γ-carbonyl boronic ester **101** with simultaneous coupling to an aryl triflate. The mechanism involves a 1,2-metallate rearrangement driven electrophilic addition of a chiral aryl palladium(II) species. The enantioenriched coupled product is then liberated through reductive elimination. While this is a powerful technique for the synthesis of functionalised γ-carbonyl boronic esters, the products are limited to those containing a benzylic group α to the boronic ester.[85]



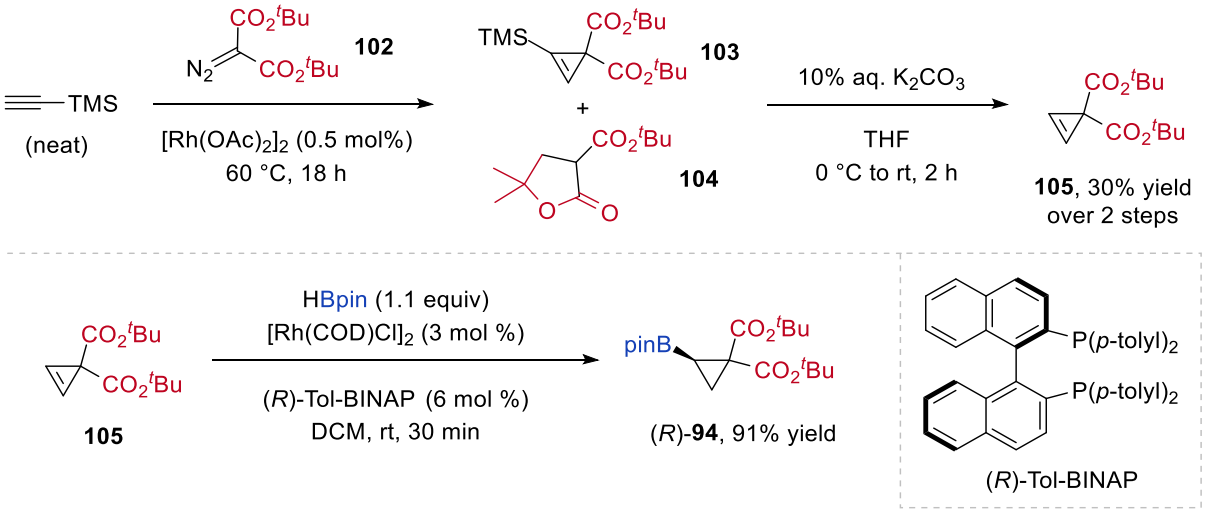
Scheme 21. Reported syntheses of enantioenriched γ-carbonyl boronic esters.

2.3. Results and discussion

2.3.1. Synthesis of di-acceptor cyclopropyl boronic ester starting material

To investigate the reactivity of an activated cyclopropyl boronate complex, the enantioselective synthesis of cyclopropyl boronic ester **94** was undertaken (Scheme 22).

A procedure for the synthesis of the equivalent di-methyl ester derivative of **94** is reported by Gevorgyan and co-workers starting from di-methyl diazo malonate.[86] A slightly modified procedure starting from di-*tert*-butyl diazo malonate (**102**) was employed in the synthesis of **94** (Scheme 22). The first step involves rhodium catalysed cyclopropenation of trimethylsilyl acetylene with di-*tert*-butyl diazo malonate. The product of this reaction is TMS substituted cyclopropene **103**.



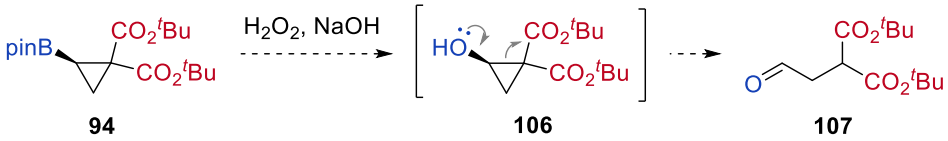
Scheme 22. Synthesis of enantioenriched di-activated cyclopropyl boronic ester **94**.

The major side product, γ-lactone **104**, is formed through an intramolecular C–H insertion reaction of the transient rhodium carbene.[87] This side-reaction was not observed by Gevorgyan and co-workers in their synthesis of the methyl ester analogue of **103**. This is because the product would be a strained β-lactone.

The next step is desilylation with K_2CO_3 to afford desired cyclopropene **105**.[86] This species was subjected to rhodium-catalysed enantioselective hydroboration to give optically active cyclopropyl boronic ester (*R*)-**94** in 91% yield. The assignment of absolute configuration is in relation to that determined by Gevorgyan and co-workers for the methyl ester analogue of **94**.[86] Racemic BINAP was employed as the ligand to synthesise (±)-**94**.

2.3.2. Determining the enantiopurity of the starting material

Cyclopropyl boronic ester **94** does not contain a UV chromophore, which prevents the determination of its enantiopurity by chiral HPLC analysis since UV detection is required. Therefore, either the derivatisation of **94**, to chemically incorporate a chromophore without interfering with the stereogenic centre, or other methods for determining enantiomeric ratio were necessary.



Scheme 23. Proposed outcome of the oxidation of boronic ester **94**.

Enantiospecific oxidation of boronic esters is a useful method to introduce a chromophore, as the corresponding alcohol can be esterified with benzoyl chloride. However, in the case of **94**, oxidation would give cyclopropyl alcohol **106** that would spontaneously rearrange to give aldehyde **107** with complete loss of stereochemical information (Scheme 23).

Gevorgyan and co-workers determined the enantiopurity of the di-methyl ester derivative of **94** by ^{1}H NMR analysis with chiral NMR shift reagent Eu(hfc)$_3$ – a chiral europium(III) complex.[86] This technique takes advantage of the formation of fluxional coordination complexes in solution between the substrate and the enantiopure shift reagent.[88] The resultant complex has two possible diastereomers, where the diastereomeric ratio corresponds to the enantiomeric ratio of the substrate. Even though the coordination complex is fluxional, resolution of the diastereomers, and thus determination of the diastereomeric ratio, can still be possible on the ^{1}H NMR timescale. However, in the case of **94**, the ^{1}H NMR signals all fall within a 0.53 ppm chemical shift range, which rendered this technique unsuitable. This is because the presence of quadrupolar Eu(hfc)$_3$ in solution causes line broadening, resulting in poor resolution of the substrate peaks ^{1}H NMR peaks.

An alternative NMR shift reagent, Pirkle's alcohol ((*R*)-(−)-1-(9-Anthryl)-2,2,2-trifluoroethanol, **108**),[89] was trialled. For reference, the ^{1}H NMR spectrum of boronic ester (±)-**94** is shown in Figure 4a between the chemical shift range of 0.8-1.6 ppm.

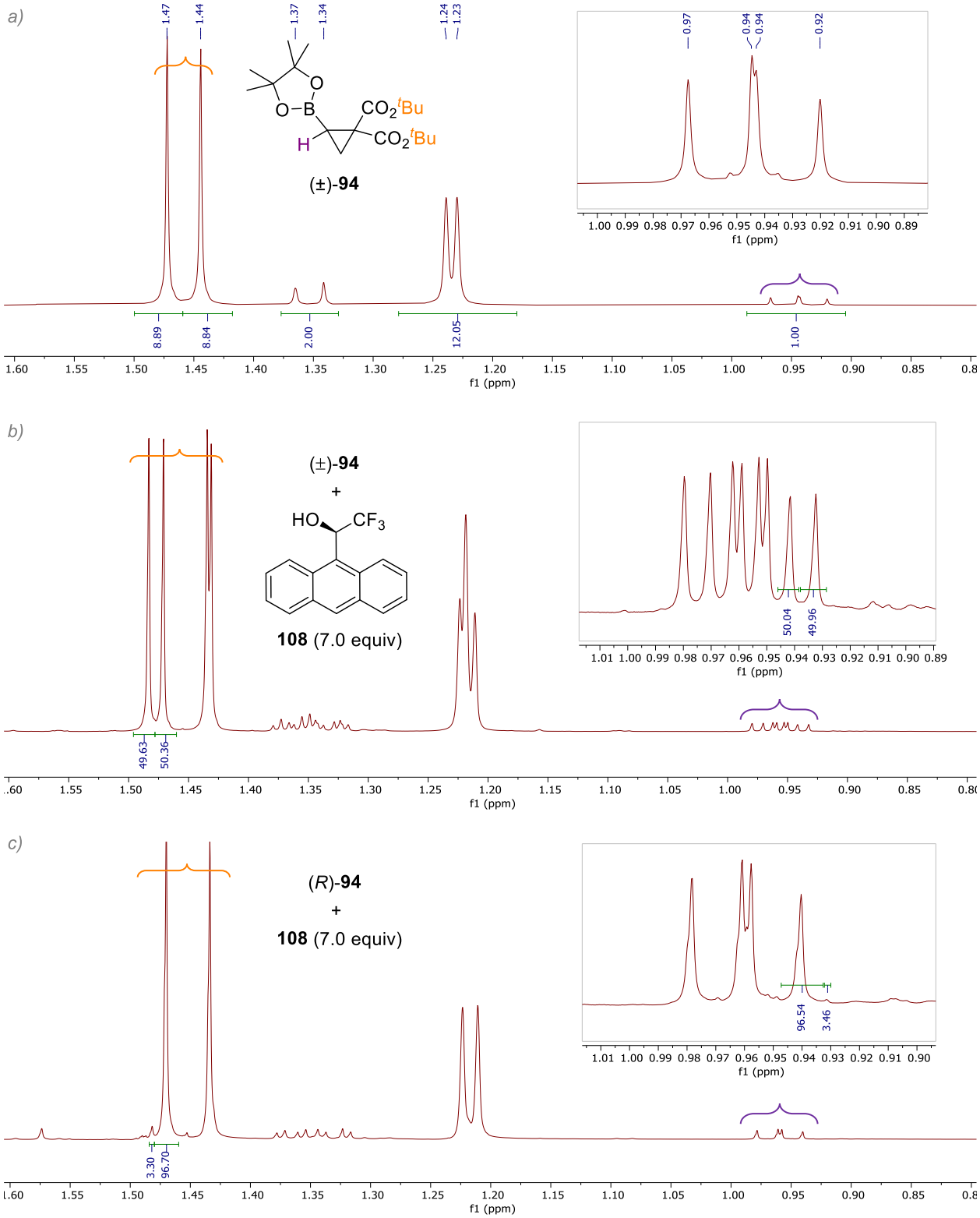


Figure 4. ^{1}H NMR spectrum in $CDCl_3$ in the region of 0.9-1.6 ppm of: a) (±)-**94**, b) (±)-**94** and (7.0 equiv) of **108** and c) (*R*)-**94** and (7.0 equiv) of **108**.

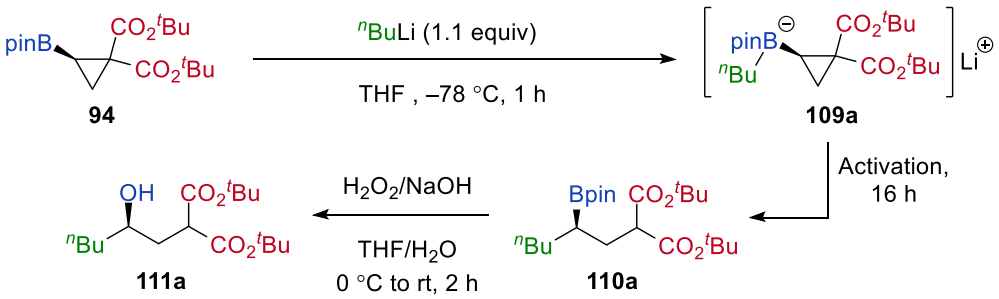
The addition of Pirkle's alcohol (**108**) causes the signals to shift and split, with the largest deviation seen in the *tert*-butyl proton signals and the α-boryl proton signal (highlighted). The splitting corresponds to the presence of both enantiomers of **94**. It was found that 7.0

equivalents of **108** were needed to give baseline separation and thus an enantiomeric ratio of 50:50 could be determined from the ^{1}H NMR by integration of the resolved signals (Figure 4b).

Performing this experiment on the enantioenriched sample of **94** gave the ^{1}H NMR spectrum shown in Figure 4c. The resolved peaks were integrated and the enantiomeric ratio was determined as 97:3. With reference to the work conducted by Gevorgyan and co-workers,[86] the expected enantiomer formed in the synthesis of **94** is *R* enantiomer.

2.3.3. Reactivity of di-acceptor cyclopropyl boronic ester

Having established a route to access highly enantioenriched boronic ester **94**, it was then treated with *n*-butyllithium. This resulted in full conversion to boronate complex **109a**, which was observed by a peak at 6 ppm in the ^{11}B NMR spectrum (Scheme 24). Despite employing a malonate to stabilize the anion resulting from the 1,2-metallate rearrangement, the boronate complex converted very slowly at room temperature to ring-opened boronic ester **110a**. Activation conditions for this transformation were then screened, accompanied by direct oxidation to alcohol **111b** using hydrogen peroxide/sodium hydroxide to aid NMR yield determination.



Scheme 24. Reaction design for the screening of activation conditions to induce a 1,2-metallate rearrangement/ring opening sequence.

The results of the reaction screening are summarised in Table 3. Under reflux conditions, boronate complex **109a** was completely consumed after 16 hours. This corresponded to the formation of ring-opened boronic ester **110a** and subsequently, alcohol **111a** was obtained in 45% NMR yield (entry 1). It was thought that in this case, the lithium counterion of the boronate complex was coordinating to the two carbonyl oxygens in a chelate which encourages the 1,2-metallate rearrangement to occur. A solvent switch to chloroform, a non-coordinating solvent, was then performed to enhance the Lewis acidity of the lithium counterion. However, these conditions led to a reduction in yield (entry 2). The addition of 2 equivalents of lithium

triflate (LiOTf) and refluxing conditions resulted in the decomposition of the boronate complex within 30 minutes (entry 3). On reducing the temperature and the equivalence of LiOTf, the reaction yield was greatly improved, and alcohol **111a** was produced in 80% yield (entry 4).

Table 3. Screening of activation conditions for the 1,2-metallate rearrangement/ring opening of boronate complex **109a**.

entry	activation conditions	NMR yield	entry	activation conditions	NMR yield
1	60 °C	45	4	LiOTf (1.0 equiv), rt[b]	80
2	$CHCl_3$, 50 °C[a]	20	5	$MgBr_2$·MeOH (1.5 equiv), rt[b]	60
3	LiOTf (2.0 equiv), 60 °C	0	6	$MgBr_2$·Et_2O (1.5 equiv), rt[b]	91[c]

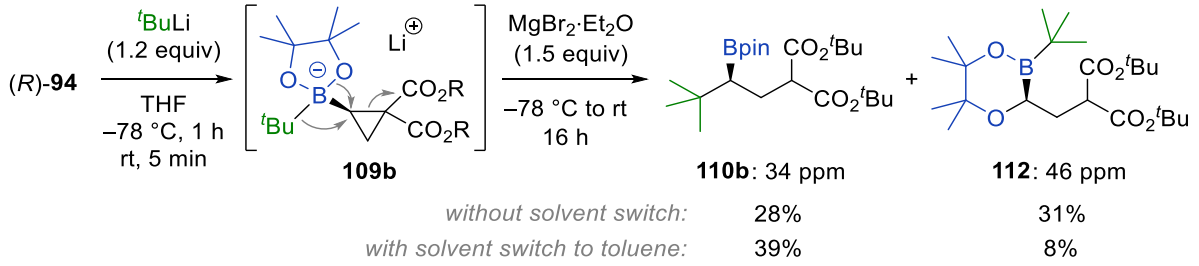
0.14 mmol scale. [a]Solvent switch to $CHCl_3$, work-up with DCM before oxidation. [b]Lewis acid addition at –78 °C, reaction was left to warm slowly to rt. [c]Isolated yield

When magnesium bromide solution in methanol ($MgBr_2$·MeOH) was used as a Lewis acid, 60% yield of **111a** was obtained (entry 5). It was found magnesium bromide etherate ($MgBr_2$·Et_2O) was optimal and led to the formation of **111a** in 91% isolated yield (entry 6). This Lewis acid is also commercially available as a solid, rendering its addition operationally simple. The enantiopurity of **111a** was found to be 97:3 er after acylation with benzoyl chloride. This result confirms that the reaction is enantiospecific (100% es), which also confirms that boronate **109a** is configurationally stable under the reaction conditions.

The 1,2-metallate rearrangement/ring opening of boronate **109a** was repeated, and after the addition of $MgBr_2$·Et_2O at –78 °C, the reaction was warmed to room temperature and transferred to an NMR tube. The conversion to boronic ester **110a** was followed by ^{11}B NMR spectroscopy and found to be complete after 3.5 hours at room temperature.

The scope of migrating groups for the 1,2-metallate rearrangement was then explored. Firstly, employing *tert*-butyllithium led to the formation of boronate complex **109b** (Scheme 25), which required warming to room temperature to ensure complete boronate complex formation of the hindered substrate. After the addition of $MgBr_2$·Et_2O, the desired product was only formed in 28% yield. This was found to be due to competing *O*-migration of one of the pinacol oxygen ligands on boron to give borinic ester **112**. Evidence for this competing process was not only the observation of characteristic signals corresponding to **112** in the crude ^{1}H NMR spectrum, but the presence of a peak at 46 ppm in the ^{11}B NMR spectrum of the reaction mixture, which is typical of a borinic ester. The side reaction of *O*-migration is thought to

compete due to the hindered nature of the *tert*-butyl group, which slows down the rate of *C*-migration.



Scheme 25. 1,2-Metallate rearrangement/ring opening reaction with *tert*-butyl migrating group.

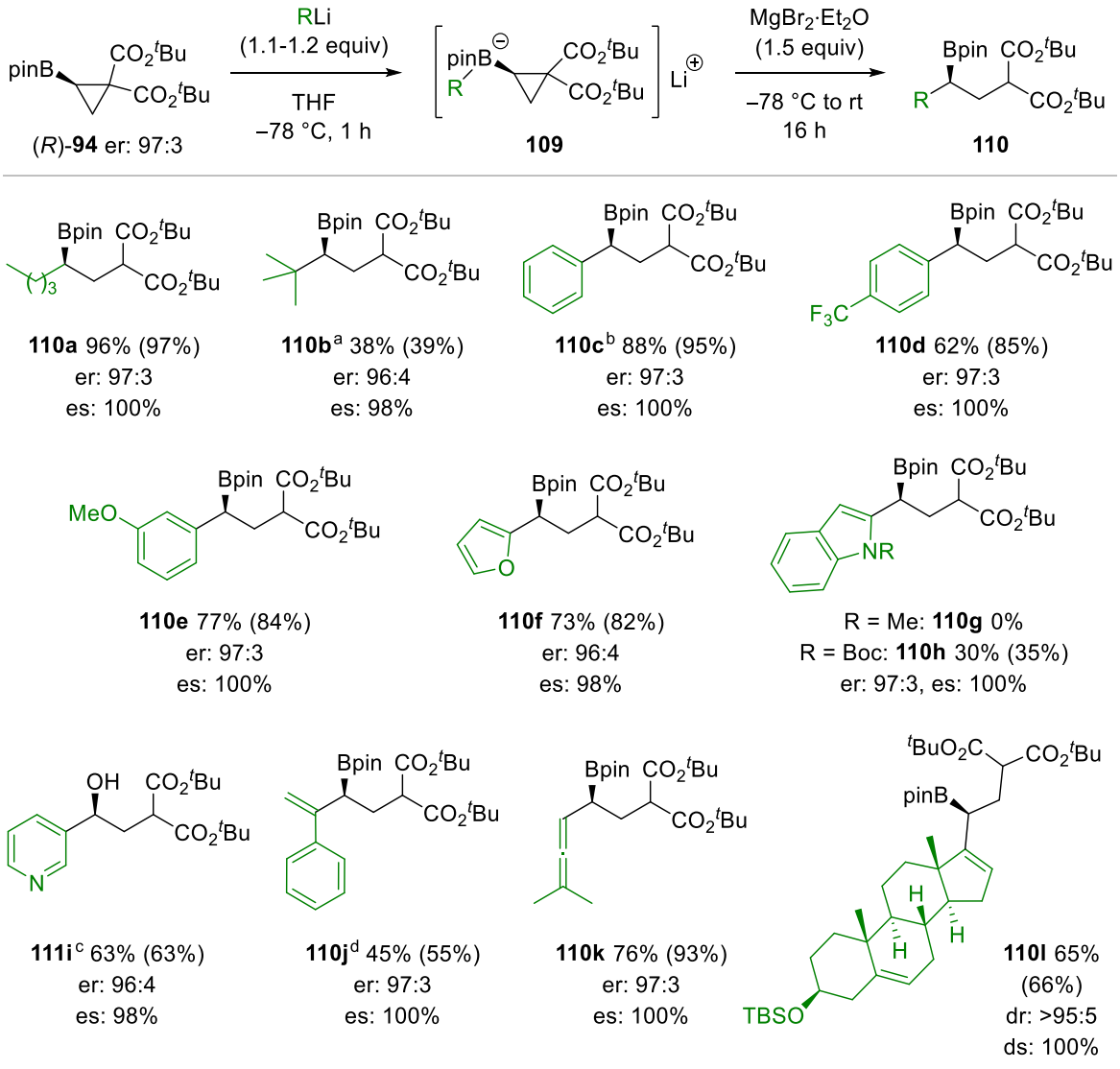
However, this side-reaction was minimized by performing a solvent switch to toluene before the addition of the Lewis acid which afforded **110b** in 38% isolated yield with 98% es.

Continuing with the reaction scope, phenyl and other aromatic migrating groups with *meta*-methoxy and *para*-trifluoromethyl substitution all performed well with good yields (88-62%) and 100% es (**110c-e**, Scheme 26). Apart from commercially available phenyllithium, the other aryllithium reagents were prepared by lithium-bromine exchange with *tert*-butyllithium from the corresponding aryl bromide. The synthesis of **110c**, was also successfully scaled to 1.09 mmol with no reduction in reaction yield. Unfortunately, due to protodeboronation on silica gel, products **110c-e** bearing a benzylic boronic ester were isolated in lower yields than determined by crude NMR.

Heteroaromatic migrating groups were then explored as substrates for this reaction. With furan-2-yllithium, prepared by the direct deprotonation of furan with *n*-butyllithium, product **110f** was obtained in 73% yield and 98% es. However, when employing lithiated *N*-methyl indole, no desired product **110g** was obtained as protodeboronation of the product had occurred before purification. Switching to lithiated *N*-Boc indole did result in the successful isolation of product **110h**, however in only moderate yield (30%). This is thought to be due to reversible boronate complex formation enabled by the high stability of the organolithium. 3-Pyridyllithium was also a successful substrate, however the boronic ester product also underwent rapid protodeboronation during aqueous work-up. In this case, it was possible to oxidise the crude reaction mixture with hydrogen peroxide/sodium hydroxide and obtain alcohol **111i** in 63% yield and 98% es.

The lithium-bromine exchange of α-bromostyrene provided access to (1-phenylvinyl)lithium, which gave allyl boronic ester **110j** in 45% NMR yield and perfect enantiospecificity. The

formation of an allenyl boronate complex was also possible by the deprotonation of 1,1-dimethyl allene followed by addition of **94**. Under the optimised activation conditions, boronic ester **110k** was formed in a good yield of 76% and 100% es.

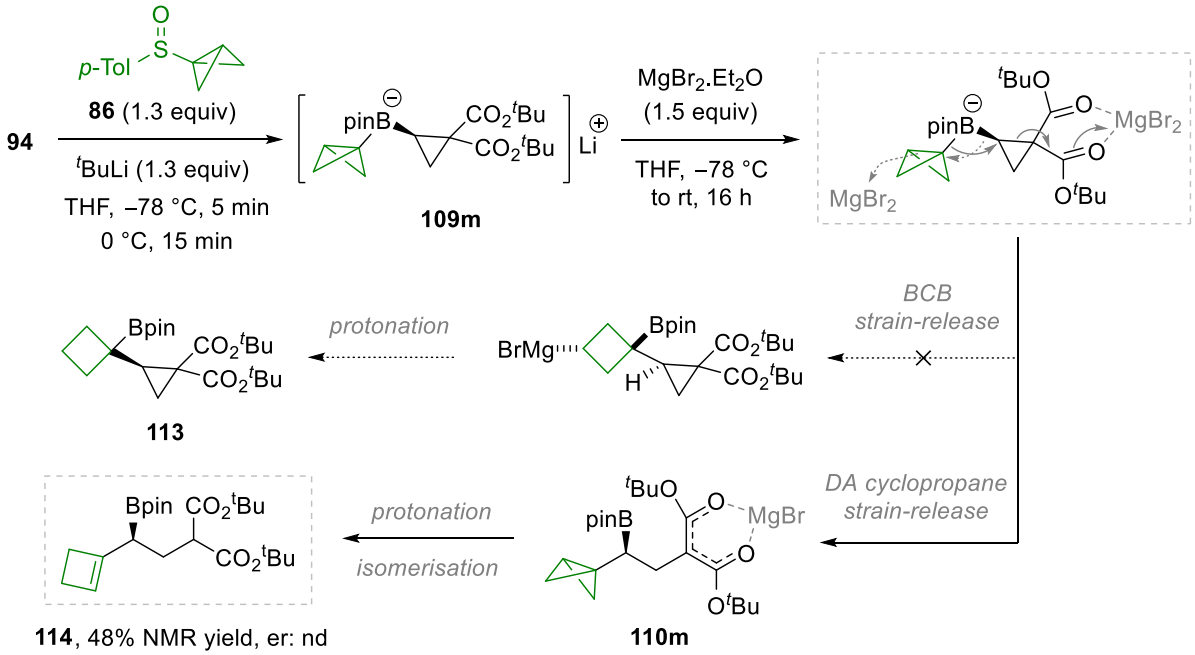


Isolated yields. NMR yields in parentheses. Reaction conditions: 0.14 mmol scale, 0.14 M, 1.1-1.2 equivalents of RLi. [a] Solvent switch to toluene before addition of $MgBr_2 \cdot Et_2O$. [b] 1.09 mmol scale, yield for 0.14 mmol scale was 78%. [c] Oxidation with H_2O_2/NaOH before work-up. [d] Oxidation with H_2O_2/NaOH after crude NMR, before column chromatography.

Scheme 26. Scope of organolithium coupling partners in the 1,2-metallate rearrangement/ring opening reaction.

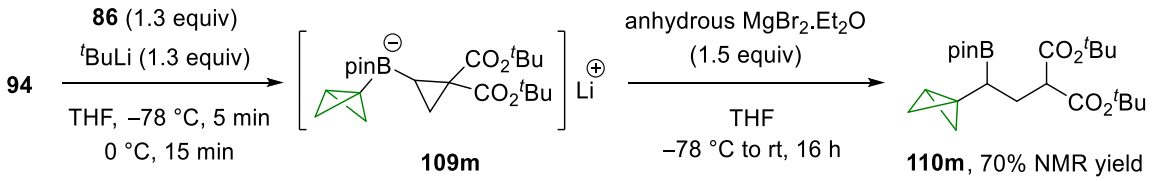
Furthermore, an iodo-steroid substrate was also suitable for the transformation. Following lithium-iodine exchange in the presence of **94**, complete conversion to the boronate complex was achieved and, under the influence of $MgBr_2 \cdot Et_2O$, gave steroid-derived boronic ester **110l** in 65% yield and 100% diastereospecificity (ds).

It was postulated that a strained structure could also act as the migrating group, and BCB was considered since BCB-Li is readily accessible from sulfoxide **86** (Scheme 27).[80] The addition of *tert*-butyllithium to a mixture of **94** and **86** resulted in the formation of boronate complex **109m**.



Scheme 27. Postulated competing pathways when BCB was employed as a migrating group.

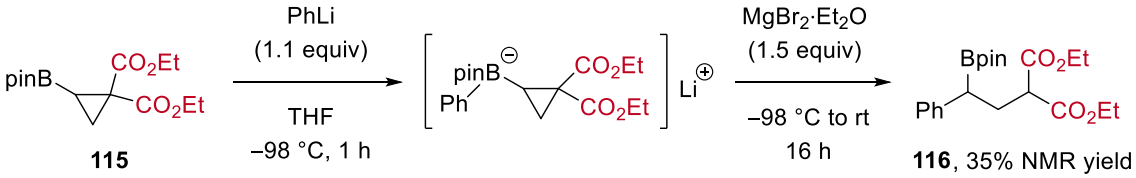
One can imagine that **109m** could undergo a 1,2-metallate rearrangement in either of two directions. If the Lewis acid activates the cyclopropane through chelation with the two carbonyl groups, the BCB substituent would migrate to give species **110m**. By contrast, if the Lewis acid instead activates the strained bridge bond of BCB, the cyclopropane substituent would migrate to give species **113** after protonation. However, the major product of this reaction was cyclobutenyl boronic ester **114**, observed in 48% NMR yield. This species does not contain an intact cyclopropane, which is evidence that the 1,2-metallate rearrangement was driven by cleavage of the cyclopropyl bond. Since the $MgBr_2 \cdot Et_2O$ used was not rigorously anhydrous, perhaps small amounts of water could act as a proton source and, under the acidic reaction conditions, could catalyse the isomerisation of **110m** to **114**. Indeed, it has since been demonstrated in a follow-up investigation by a fellow research group member that using freshly prepared, anhydrous magnesium bromide solution in diethyl ether, boronic ester **110m** is formed in 70% NMR yield (Scheme 28).



Scheme 28. BCB as a successful migrating group under anhydrous conditions.

This dominant direction of reactivity of the boronate complex can be reasoned in two ways. Firstly, the interaction of magnesium with chelating oxygen atoms is more favourable than with a C–C bond. In addition, the migratory aptitude of each alkyl substituent on boron should be considered. The cyclopropyl substituent contains two electron withdrawing groups so is likely to be less nucleophilic than the BCB substituent. It is thought that these two effects contribute to the formation of boronic ester **110m**.

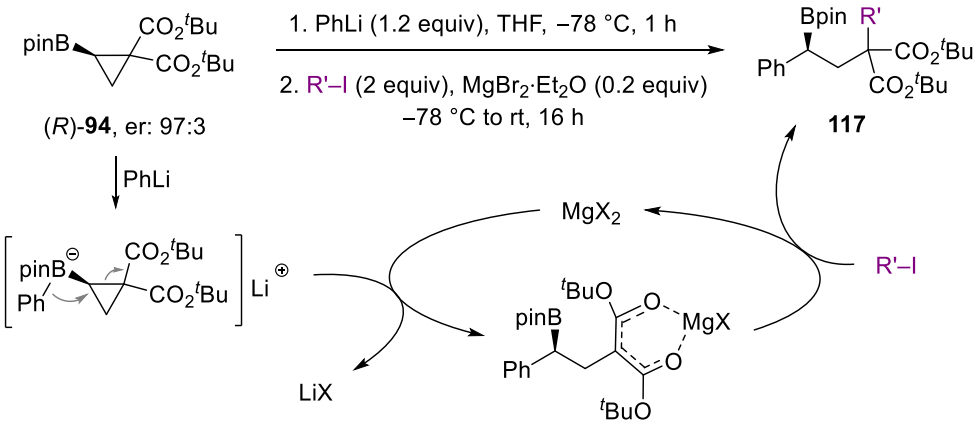
Boronic ester **94** was originally chosen as a substrate as undesired 1,2-addition of the organolithium reagent to the carbonyl is unlikely to occur with the hindered *tert*-butyl esters. However, boronic esters are very Lewis acidic and a boronate complex has been known to form when phenyllithium is added to a boronic ester containing a less hindered ester group.[90] To evaluate whether *tert*-butyl esters are a necessity in this reaction, boronic ester **115** comprising diethyl esters was employed (Scheme 29). In this case, the temperature was lowered to −98 °C to limit 1,2-addition, however ring-opened product **116** was observed in only 35% NMR yield, in comparison to 95% NMR yield for the *tert*-butyl ester analogue.

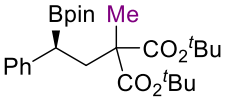
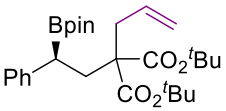
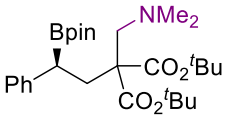


Scheme 29. Reactivity of cyclopropyl boronic ester comprising two ethyl ester functional groups.

2.3.4. Three-component reaction with catalytic Lewis acid

It was expected that the enolate formed after 1,2-metallate rearrangement could be trapped with electrophiles *in situ* in a three-component coupling process. This approach is prevalent in reports of nucleophilic addition to DA cyclopropanes as it provides enhanced efficiency and enables sub-stoichiometric quantities of the Lewis acid to be employed.[19–24,76] The use of anhydrous Lewis acid is a necessity to avoid protonation of the enolate. In our case it was operationally simpler to weigh out solid $MgBr_2 \cdot Et_2O$ in a nitrogen atmosphere glovebox than to freshly prepare it as an anhydrous solution.



R'–I	product	R'–I	product	R'–I	product
MeI	 **117a** 77% (81%) er: 97:3 es: 100%		 **117b** 88% (99%) er: 97:3 es: 100%	 **118**	 **117c**[a] 72% (81%) er: 97:3 es: 100%

Reaction conditions: 0.14 mmol scale, 0.14 M. [a]Oxidation with H_2O_2/NaOH after crude NMR, before column chromatography.

Scheme 30. Scope of electrophiles for *in situ* functionalisation.

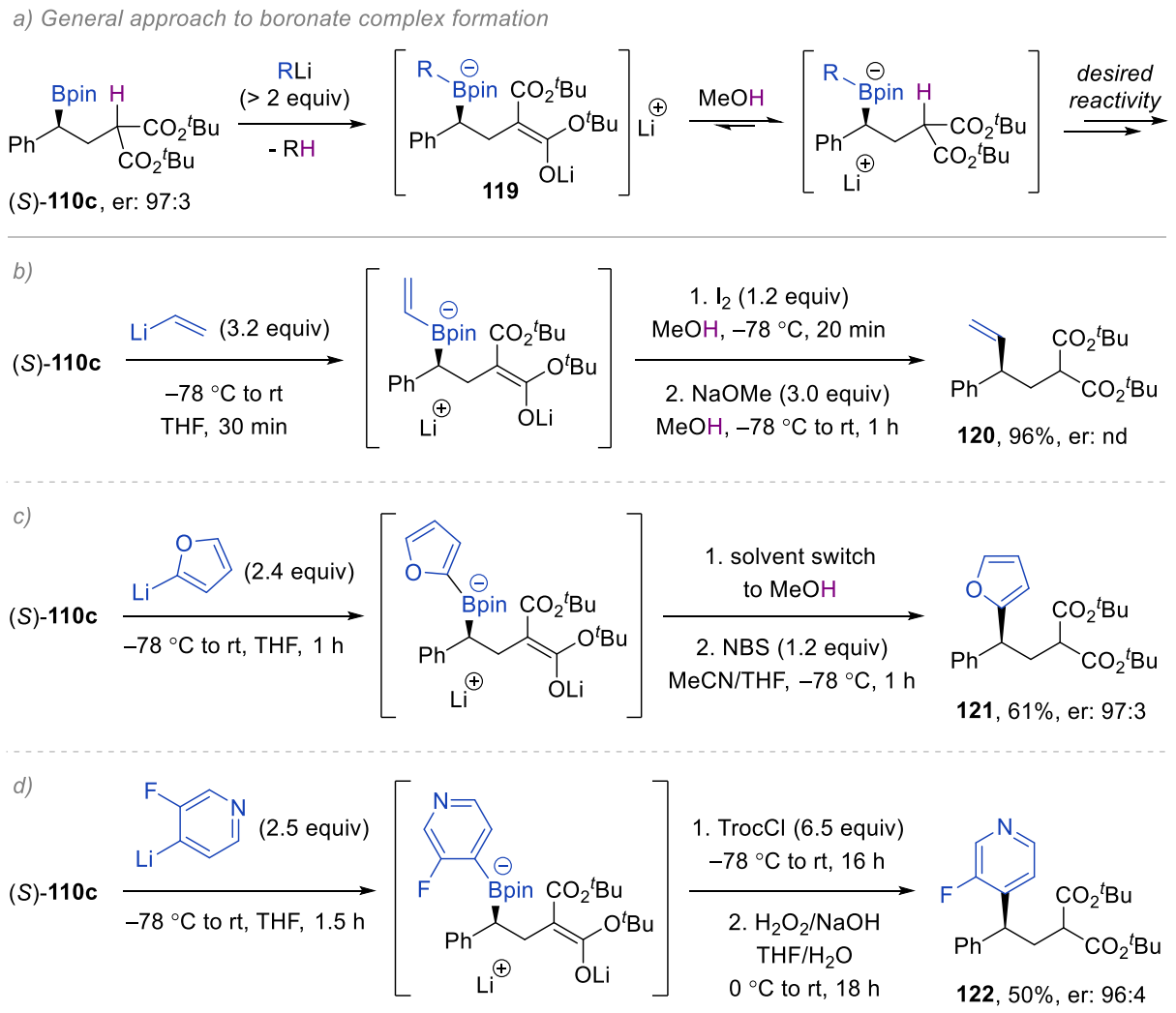
With this modification, initial attempts showed that the reaction was feasible with 20 mol% $MgBr_2{\cdot}Et_2O$ in the presence of methyl iodide as the electrophile. This gave methylated product **117a** in 77% yield and 100% es (Scheme 30).

Allyl iodide and Eschenmoser's salt (**118**) were also successfully employed as electrophiles giving **117b** and **117c** in 88% and 72% yield respectively with complete enantiospecificity.

2.3.5. Product functionalisation

It was important to evaluate the synthetic utility of the enantioenriched γ-carbonyl boronic esters synthesised using this methodology. However, many enantiospecific transformations of alkyl boronic esters begin with the addition of an organolithium reagent to access a boronate complex.[58] This is problematic for the boronic esters shown in Scheme 26 as they possess an acidic malonate functional group. It was therefore necessary to modify existing procedures and account for the acidic group by using additional equivalents of organolithium reagent to form di-anionic boronate complexes such as **119** (Scheme 31a).

If necessary, the enolate component of the di-anionic boronate complex could then be protonated, with a proton source such as methanol, to provide the desired boronate complex for further reactivity.

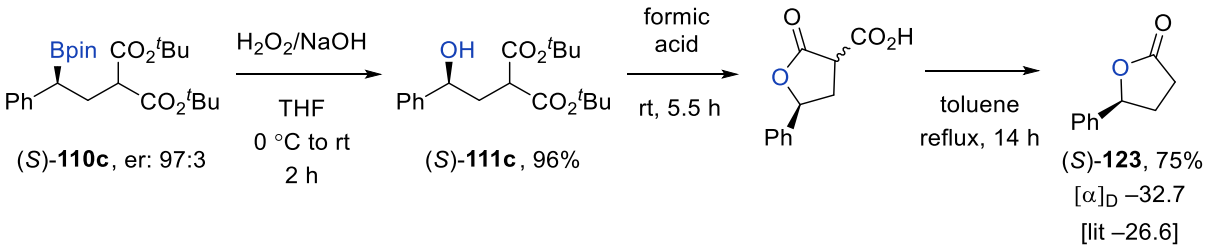


Scheme 31. Enantiospecific transformations of γ-carbonyl boronic ester **110c**.

With boronic ester **110c** (Scheme 31b) Zweifel olefination was possible with 3.2 equivalents of vinyllithium and methanol added as a proton source. Upon addition of iodine/methanol, followed by sodium methoxide, alkene **120** was obtained in 96% yield.[68] Similarly, sp^2-sp^3 coupling to furan with 2.4 equivalents of furan-2-yllithium followed by a solvent switch to methanol and addition of NBS gave desired product **121** in 61% yield (Scheme 31c).[70] Furthermore, sp^2-sp^3 coupling to 3-fluoropyridine was also achieved with 2.5 equivalents of (3-fluoropyridin-4-yl)lithium (Scheme 31d). The 1,2-migration was triggered upon addition of TrocCl and oxidation with sodium hydroxide/hydrogen peroxide gave coupled product **122** in 50% yield.[72] Exploring these modifications for boronic ester **110c** has consequently broadened

the scope of these existing enantiospecific transformations to tolerate an acidic functional group.

The enantiospecific oxidation of boronic ester **110c** yielded alcohol **111c** (Scheme 32). This compound was then subjected to hydrolysis and lactonization with formic acid and subsequent thermal decarboxylation to give γ-phenyl-γ-butyrolactone (**123**).[91] The optical rotation of **123** corresponded to that reported for the *S* enantiomer which confirmed that the absolute stereochemistry of boronic ester **110c** is *S*.[92,93] This confirms that the 1,2-metallate rearrangement/ring opening sequence of cyclopropyl boronate complexes proceeds through inversion of stereochemistry at the α-boryl carbon.

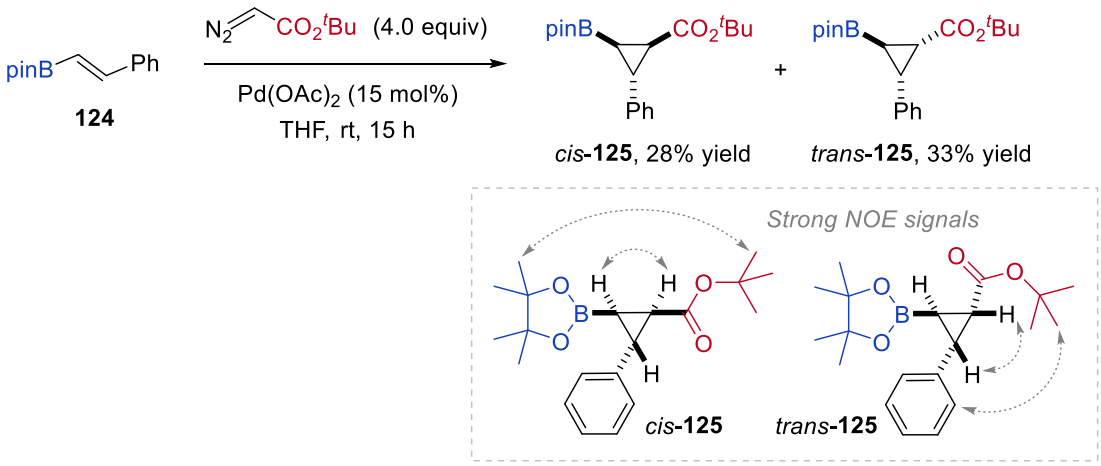


Scheme 32. Determination of absolute configuration of γ-carbonyl boronic ester **110c**.

2.3.6. Synthesis of mono-acceptor cyclopropyl boronic ester

It was established that the cyclopropyl boronate complex with two electron withdrawing groups can undergo 1,2-metallate rearrangement/ring opening thermally or by activation with a Lewis acid. The necessity for two electron withdrawing groups was then investigated.

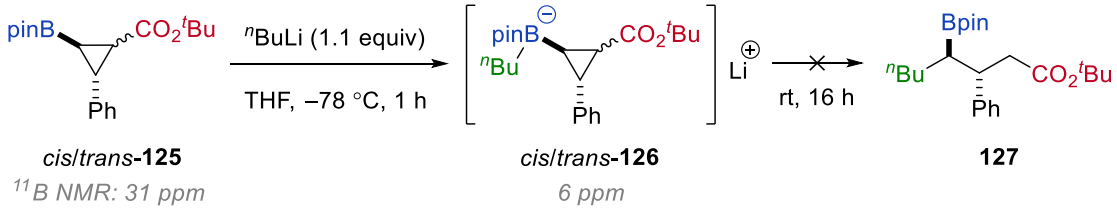
Cyclopropyl boronic esters *cis*/*trans*-**125** were chosen as model starting materials, bearing a phenyl substituent to lower the volatility of the product and aid in its isolation (Scheme 33). *Cis*- and *trans*-**125** were synthesised using palladium-catalysed cyclopropanation of styryl pinacol boronic ester **124** with *tert*-butyl diazo acetate.[94,95] This reaction yielded both diastereomers in close to a 1:1 ratio, which were separable by silica gel chromatography. Both isomers have the boronic ester and the phenyl substituent on opposite sides of the cyclopropane as this geometry was already set in *trans* alkene **124**. The diastereomers differ based on which side the ester substituent is situated. The diastereomer with the ester group on the same side as the boronic ester was labelled the *cis* isomer and the diastereomer with the ester group on the opposite side as the boronic ester was labelled the *trans* isomer. The configurations of each were assigned based on NOE signals.



Scheme 33. Palladium catalysed cyclopropanation of styryl pinacol boronic ester with *tert*-butyl diazo acetate. NOE signals to determine the configuration of each diastereomer.

2.3.7. Reactivity of the mono-acceptor cyclopropyl boronic ester

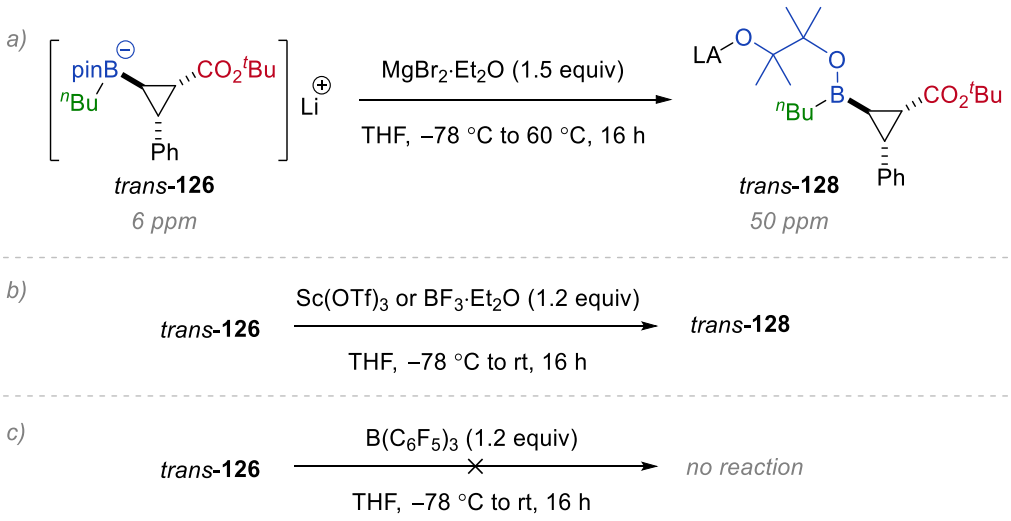
On treatment of each isomer of **125** with *n*-butyllithium, conversion to boronate complex **126** was observed by the presence of a peak at 6 ppm in the ^{11}B NMR spectrum (Scheme 34). However, in contrast to the boronate complex with two ester substituents (**109**), there was no change in the ^{11}B NMR spectrum after 16 hours at room temperature and thus no thermal 1,2-metallate rearrangement/ring opening. It was evident that stronger activation conditions would be required to cleave the less activated cyclopropane C–C bond to yield desired product **127**.



Scheme 34. Treatment of mono-activated cyclopropyl boronic ester with *n*-butyllithium.

Activation conditions were then screened separately for each isomer. Attempts to activate boronate complex *trans*-**126** with Lewis acids are shown in Scheme 35. The first conditions chosen were the addition of solid $MgBr_2 \cdot Et_2O$ at –78 °C and subsequent warming to 60 °C for 16 hours (Scheme 35a). The formation of borinic ester *trans*-**128** was observed by a peak at 50 ppm in the ^{11}B NMR spectrum of the reaction mixture. This is evidence that the Lewis acid coordinates preferentially to one of the pinacol oxygen atoms rather than the carbonyl oxygen atom, which causes cleavage of a B–O bond. Due to the instability of borinic esters to aqueous work-up and column chromatography, only some starting material *trans*-**125** was recovered

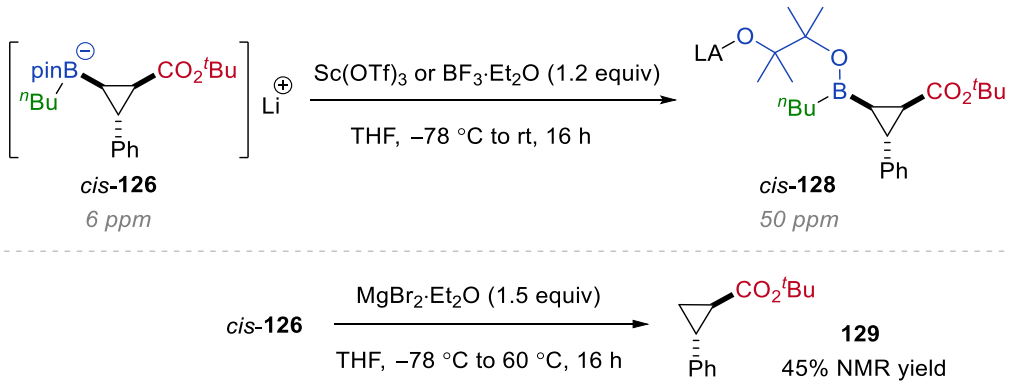
with no formation of desired product **127** observed. The same reactivity was observed for Lewis acids scandium triflate ($Sc(OTf)_3$) and boron trifluoride diethyl etherate ($BF_3{\cdot}Et_2O$) at room temperature (Scheme 35b).



Scheme 35. Attempted Lewis acid activation of the mono-activated cyclopropyl boronate complex *trans*-**126**.

It was speculated that the carbonyl oxygen atom is less hindered than the pinacol oxygen atoms as it is 3 bonds from a quaternary carbon rather than 1 bond. Therefore, a hindered Lewis acid was trialled in the hope that the difference in steric hinderance could influence the chemoselectivity to give preferential carbonyl activation to facilitate the 1,2-metallate rearrangement/ring opening reaction. Tris(pentafluorophenyl)borane ($B(C_6F_5)_3$) has comparable Lewis acidity to BF_3 but is considerably more sterically hindered.[96] However, employing this Lewis acid to the activation of boronate complex *trans*-**126** gave no reactivity after 16 hours at room temperature (Scheme 35c). The boronate complex was consumed after 26 hours at 60 °C, however, no desired ring-opened product was formed and only decomposition of the boronate complex had occurred.

The reactivity of *cis*-**126** was then investigated. Once again, the addition of either Lewis acids $Sc(OTf)_3$ or $BF_3{\cdot}Et_2O$ led to borinic ester formation (Scheme 36). In the case of $MgBr_2{\cdot}Et_2O$, different reactivity to the *trans* isomer was observed. The major product of the reaction was the protodeboronation product **129** formed in 45% NMR yield. However, in all cases, no ring-opened products were observed.

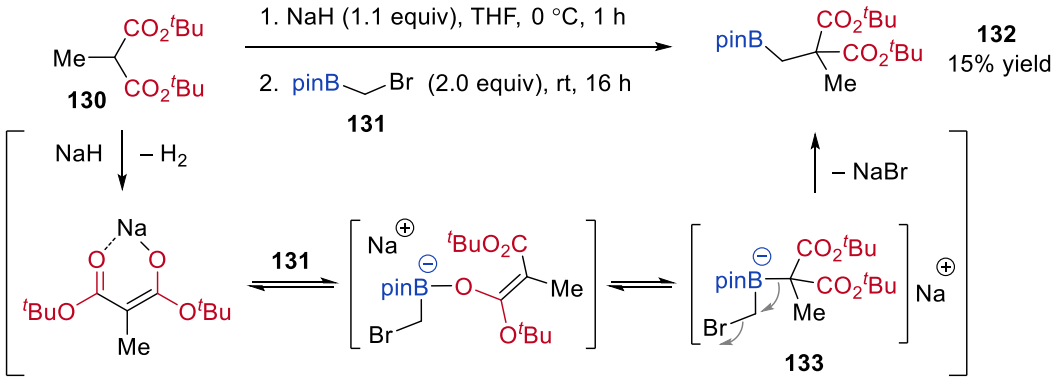


Scheme 36. Attempted Lewis acid activation of the mono-activated cyclopropyl boronate complex *cis*-**126**.

2.3.8. Reactivity study

With the knowledge that two acceptor groups are required for the desired 1,2-metallate rearrangement mechanism to occur, it was considered whether the C–C bond α to the boronate needed to be part of a strained ring. To investigate this, boronic ester **132** with an open chain structure and two *tert*-butyl ester groups was chosen as a suitable substrate.

To synthesise **132**, di-*tert*-butyl 2-methylmalonate (**130**) was deprotonated with sodium hydride and the resultant enolate reacted with boronic ester **131** (Scheme 37). The formation of desired boronate complex **133** is likely reversible due to high steric hinderance around boron and the relative stability of the enolate. However, when boronate **133** is formed, a 1,2-metallate rearrangement can occur with loss of bromide to give desired product **132**, albeit in low yield.[97]

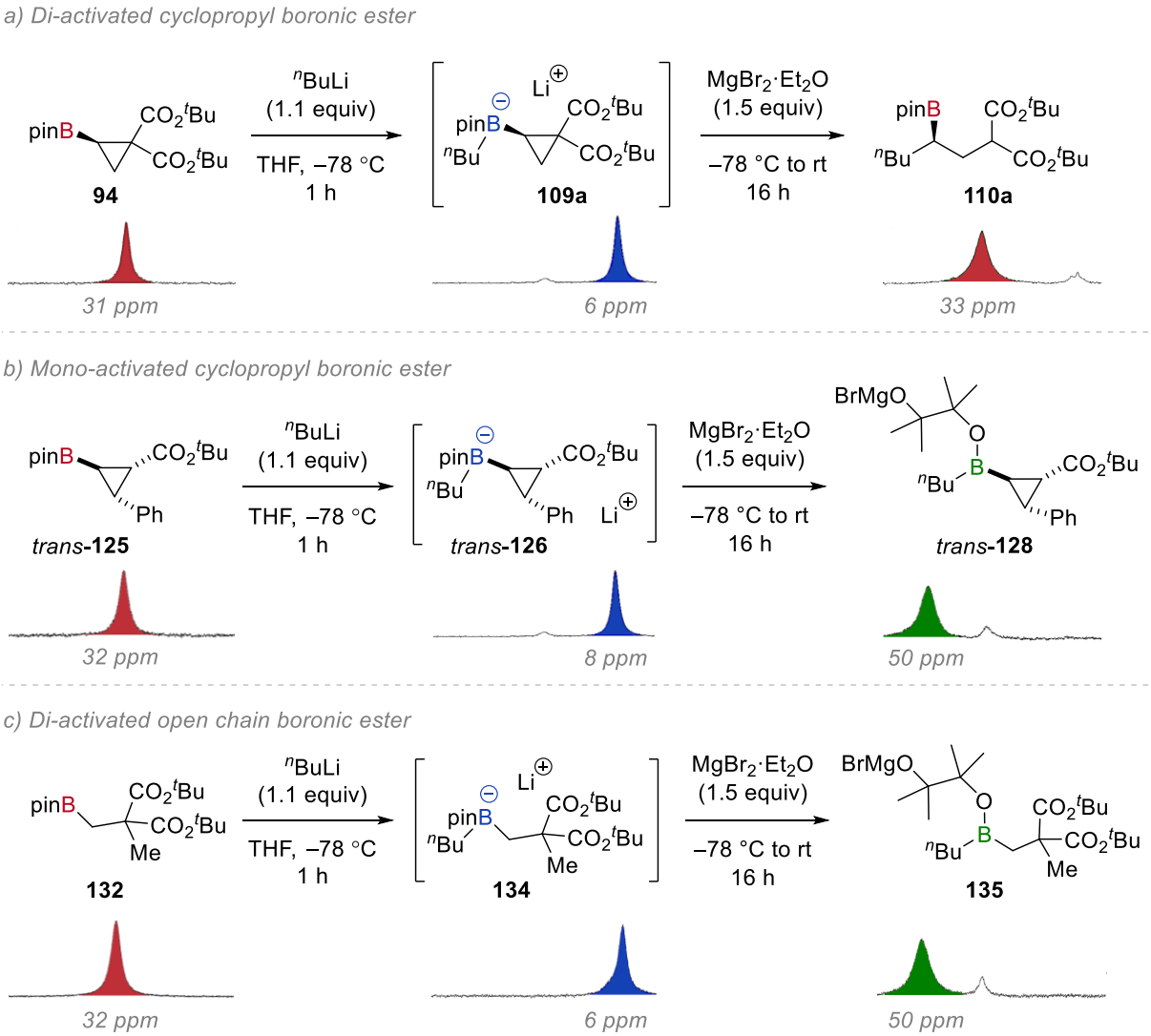


Scheme 37. Synthesis of di-acceptor open chain boronic ester **132**.

For reference, the reaction of di-acceptor cyclopropyl boronic ester **94** with *n*-butyllithium was followed by ^{11}B NMR spectroscopy (Scheme 38a). Full conversion to boronate complex **109a** was observed by a shift to 6 ppm in the ^{11}B NMR spectrum. After the addition of $MgBr_2{\cdot}Et_2O$

and stirring at room temperature for 16 hours, the ^{11}B NMR spectrum had one major peak at 33 ppm. This corresponds to the formation of sp^3 hybridised boronic ester **110a**.

As previously described, the reaction sequence for mono-acceptor cyclopropyl boronic ester *trans*-**125** also proceeds through a boronate complex, however the addition of $MgBr_2{\cdot}Et_2O$ led to the formation of borinic ester *trans*-**128**, identified by a characteristic ^{11}B NMR chemical shift at 50 ppm (Scheme 38b). The reactivity of di-acceptor open chain boronic ester **132** was then investigated and compared to these previous reactions (Scheme 38c). Again, after formation of boronate complex **134**, addition of $MgBr_2{\cdot}Et_2O$ led to the formation of a borinic ester (**135**). As with the reaction of boronate *trans*-**126**, no evidence of the 1,2-metallate rearrangement product was detected in the crude ^1H NMR spectrum.



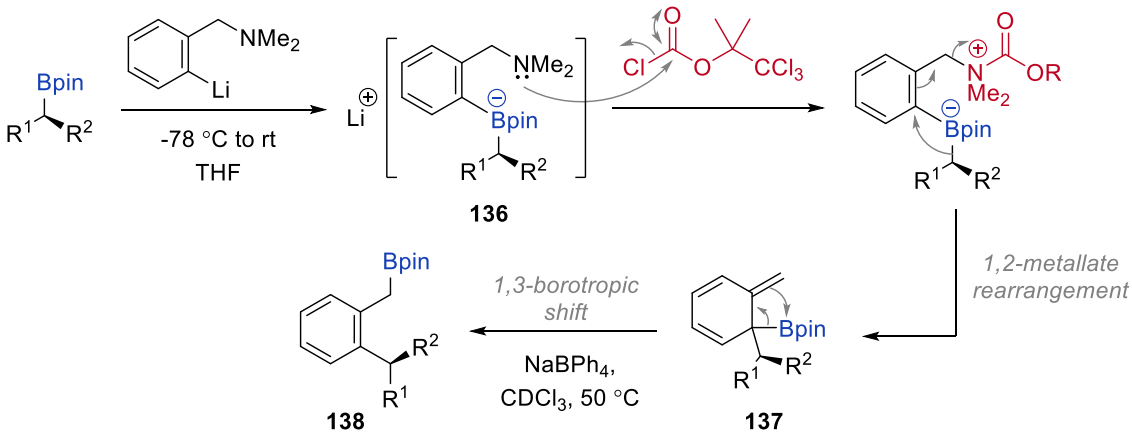
Scheme 38. Reactivity of different β-carbonyl boronate complexes with $MgBr_2{\cdot}Et_2O$ studied by ^{11}B NMR spectroscopy.

The shared reactivity of boronate complexes *trans*-**126** and **134**, which is orthogonal to the reactivity of boronate complex **109**, demonstrates that both strain-release and the presence of two ester groups are necessary to drive the 1,2-metallate rearrangement. Without either structural feature, borinic ester formation dominates.

2.3.9. Attempted dearomative 1,2-metallate rearrangement of an aryl cyclopropyl boronic ester

2.3.9.1. Reaction proposal and experiment design

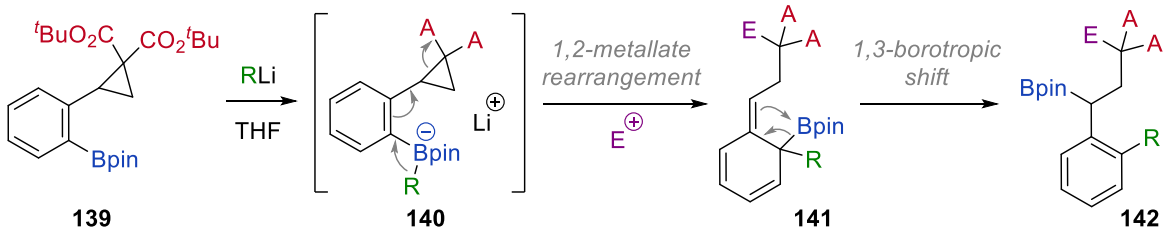
As discussed previously in section 2.1.3, an analogue of the Matteson homologation is possible where the boronate centre and the leaving group are not adjacent to each other but distal and in conjugation. This is referred to as the vinylogous Matteson homologation and a specific example is shown in Scheme 39. Here, the 1,2-metallate rearrangement of aryl boronate complex **136** is induced by the presence of a benzylic leaving group in the *ortho*-position. The 1,2-metallate rearrangement of **136** proceeds through dearomatized intermediate **137**. This species was isolable but could further undergo a Lewis acid catalysed 1,3-borotropic shift to afford *ortho*-substituted benzylic boronic ester **138**.



Scheme 39. Sp^2-sp^3 coupling of boronic esters with *ortho*-lithiated benzylamines.

It was hypothesised that a vinylogous variant of the cyclopropane ring opening reaction investigated herein could be possible. A boronate complex such as **140** could undergo such a transformation whereby the activation of the cyclopropane acceptor groups with a Lewis acid could trigger a dearomative 1,2-metallate rearrangement to give boronic ester **141** (Scheme 40). Analogous to the literature example in Scheme 39, this species could also undergo a 1,3-borotropic shift to give γ-carbonyl boronic ester **142**. Boronate complex **140** could be easily accessed by the addition of an organolithium reagent to boronic ester **139**. Although similar to

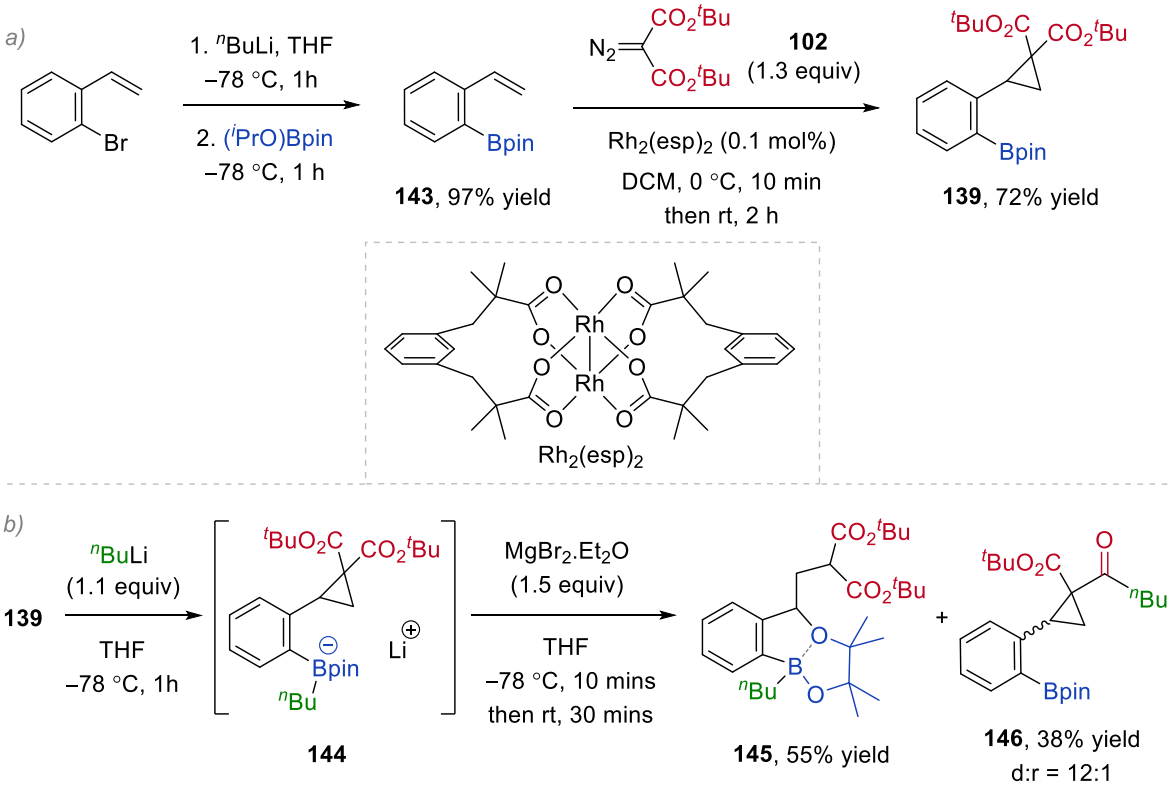
previously synthesised **94**, **139** instead has the boronic ester and cyclopropane in conjugation rather than bonded directly to eachother.



Scheme 40. Proposed dearomative 1,2-metallate rearrangement/ring opening reaction and subsequent 1,3-borotropic shift to give functionalised γ-carbonyl boronic esters.

2.3.9.2. Synthesis and reactivity of 2-cyclopropylphenyl boronate complex

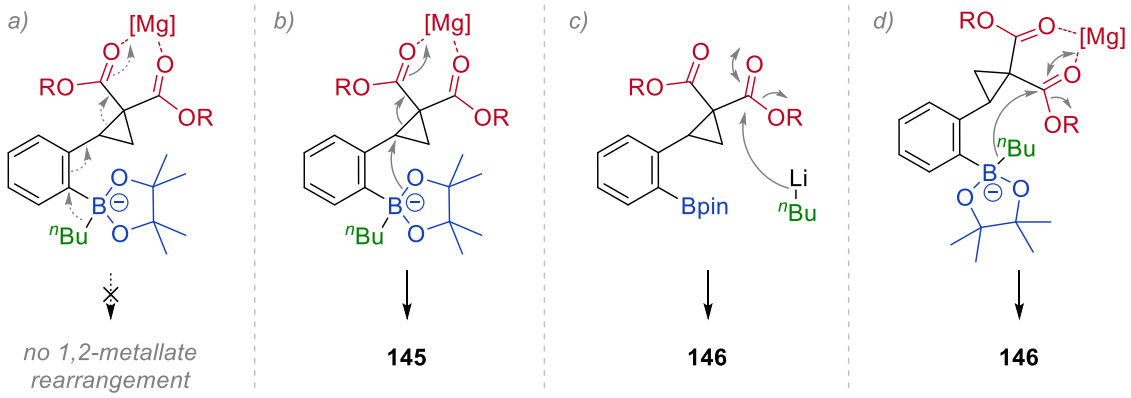
The racemic synthesis of aryl boronic ester **139** was undertaken (Scheme 41a). Firstly, boronic ester **143** was accessed by the lithium-halogen exchange of 2-bromostyrene with *n*-butyllithium. This species was trapped *in situ* with *iso*-propoxy pinacol borate to afford **143** in 97% yield. Cyclopropanation with di-*tert*-butyl diazo malonate (**102**) and catalytic $Rh_2(esp)_2$ gave **139** in 72% yield.[98]



Scheme 41. Synthesis of 2-cyclopropylphenyl boronate complex **139** and subsequent attempted 1,2-metallate rearrangement/ring opening reaction.

Boronic ester **139** was treated with *n*-butyllithium at –78 °C to give boronate complex **144**, followed by $MgBr_2 \cdot Et_2O$ (Scheme 41b). After 30 minutes at room temperature, no boronate complex was observed by ^{11}B NMR spectroscopy. Two major products were formed in this reaction, 8-membered ring containing borinic ester **145** and boronic ester **146** (Scheme 41b). It appears that after the formation and activation of boronate **144** with magnesium bromide, the desired dearomative 1,2-metallate rearrangement (Scheme 42a) does not occur. Instead, one of the pinacol oxygen atoms undergoes a 1,4-migration to the electrophilic carbon of the DA cyclopropane to give **145** (Scheme 42b). Borinic ester **145** has a ^{11}B NMR chemical shift of 26 ppm. This is considerably lower than the typical chemical shift of 50 ppm for a borinic ester. In addition, **145** was isolated after column chromatography. This is despite the expected instability of borinic esters on silica gel due to their greater electrophilicity than boronic esters. These two pieces of evidence suggest that the oxygen lone pair of the ether in **145** coordinates to boron thus reducing its electrophilicity and ^{11}B NMR chemical shift.

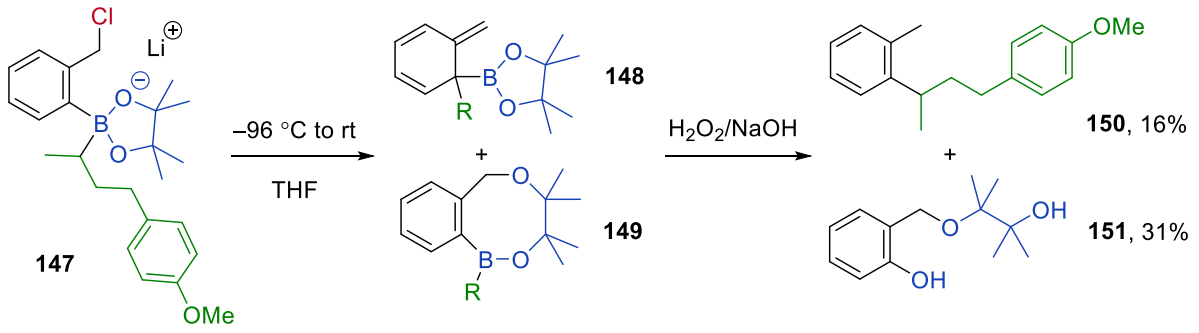
The formation of ketone **146** under the reaction conditions is intriguing, as *n*-butyllithium appears to have undergone a 1,2-addition to one of the *tert*-butyl esters (Scheme 42c). This is unexpected as the carbonyl carbon is very hindered and such reactivity has not been observed with previous cyclopropyl boronic esters bearing a *tert*-butyl ester. However, the boron in **139** is also in the hindered *ortho*-position which may reduce the rate of borylation. Another explanation is that after activation of the carbonyl with magnesium bromide, an intramolecular nucleophilic addition of the *n*-butyl group occurs (Scheme 42d). In this case, the aryl boronate complex would be acting as a nucleophilic organometallic reagent which is reported reactivity.[84,99]



Scheme 42. Possible competing reaction mechanisms from cyclopropyl boronate complex **144**.

There is also precedent for the formation of borinic ester **145**. Similar reactivity has been observed previously by another research student in the Aggarwal group (Scheme 43).[100] In this

case, aryl boronate complex **147**, which contains a chloride leaving group in the benzylic position, was investigated to see if a dearomative 1,2-metallate rearrangement would occur upon warming to room temperature to give boronic ester **148**. After *in situ* oxidation, desired product **150** was isolated; the boronate complex had indeed undergone the 1,2-metallate rearrangement followed by boron elimination/aromatisation, albeit in a low yield. However, the major product was diol **151** derived from borinic ester **149**, which is formed by the same 1,4-*O*-migration mechanism.



Scheme 43. Literature reported example of the occurrence of a similar undesired 1,4-*O*-migration reaction.

The various aryl boronate complexes with benzylic leaving groups that have been investigated to date in the Aggarwal group are shown in Figure 5.[74] It is remarkable that the nature of the leaving group has such a large effect on reactivity, to the extent that boronate **152** undergoes a completely different reaction mechanism to boronate **153**. Effects that could dictate which reaction mechanism operates are the steric hindrance at the benzylic position or perhaps the favoured conformational geometry adopted by the boronate complex.

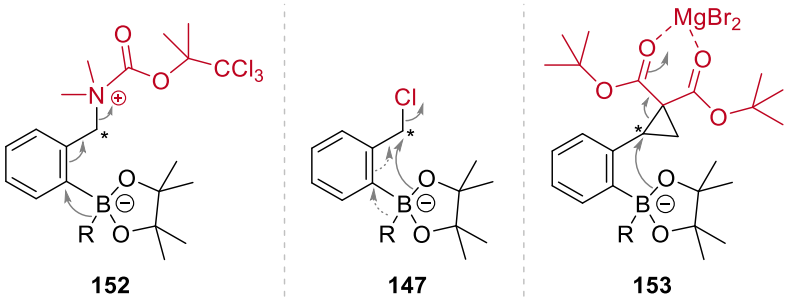
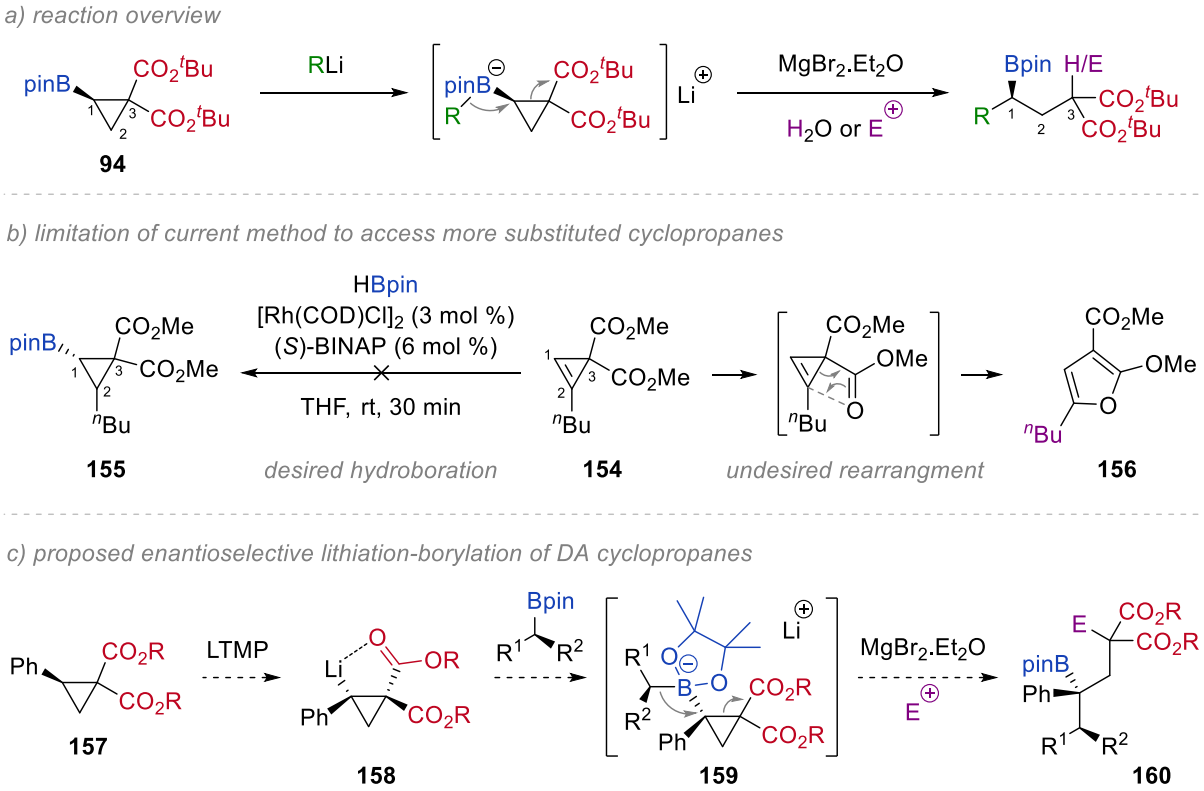


Figure 5. Comparison between phenyl boronate complexes with 2-substituted benzylic leaving groups.

2.3.10. Conclusion and future work

This chapter has described investigations into the chemistry of activated cyclopropyl boronate complexes.[82] The Lewis acid facilitated stereospecific 1,2-metallate rearrangement/ring opening of a cyclopropyl boronate complex comprising two electron withdrawing groups has

been developed (Scheme 44a). This reaction produces γ-carbonyl boronic esters in good to excellent yields. A scope of organolithium reagents has been presented with successful examples including alkyl, aryl, vinyl and heteroaryl migratory groups. The use of a substoichiometric quantity of Lewis acid in the presence of an electrophile enabled concurrent functionalisation at the C3 carbon. A γ-carbonyl boronic ester product was shown to successfully undergo enantiospecific sp^2-sp^3 coupling reactions with vinyllithium, furan-2-yllithium and (3-fluoropyridin-4-yl)lithium. These reactions proceeded with good yields and demonstrated that the γ-carbonyl boronic esters can be used as effective chiral molecular building blocks.



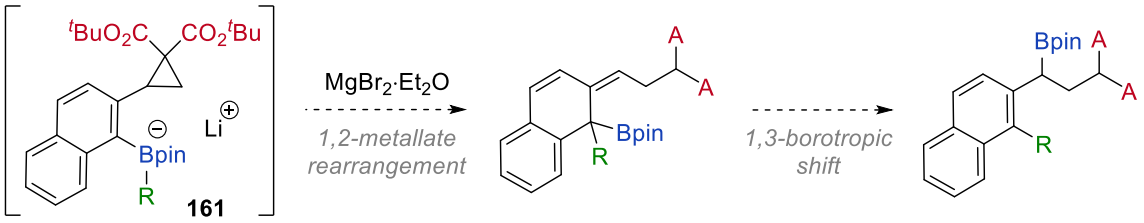
Scheme 44. Reaction overview, limitation of starting material synthesis and possible future work.

The 1,2-metallate rearrangement/ring opening sequence was found to only proceed if the cyclopropane was substituted with two carboxylate groups. In addition, the driving force of strain-release was also found to be necessary for the reaction to occur.

While the reactivity of cyclopropyl boronate complexes derived from **94** has been established, the scope is limited to starting material **94** without further substitution at C1 or C2 (Scheme 44a). Gevorgan and co-workers reported that the hydroboration of cyclopropene **154** to give cyclopropyl boronic ester **155** was unsuccessful due to a competing rearrangement mechanism that gave thermodynamically more stable furan **156** (Scheme 44b). Therefore, more substituted

starting materials are not accessible using this method. Still unexplored is the possibility of accessing a cyclopropyl boronate complex by the lithiation–borylation of DA cyclopropanes such as **157** (Scheme 44c). It would be interesting to see if a hindered base, such as LTMP, is able to deprotonate **157** in the benzylic position which would be directed by one of the ester carbonyl groups to give **158** and whether such a species is configurationally stable. The addition of an enantioenriched alkyl boronic ester to **158** would give boronate complex **159**. After 1,2-metallate rearrangement/ring opening, boronic ester product **160** would contain two contiguous stereocentres.

The desired transformation from 2-cyclopropylphenyl boronic ester complex **139** has an energy barrier associated with the loss of stability due to dearomatisation. In the case of 2-cyclopropylnaphthyl boronate complex **161** (Scheme 45), the energy cost associated with dearomatisation is lower. Therefore, in this system, the 1,2-metallate rearrangement pathway may be favoured over the *O*-migration pathway. However, the second step involving a 1,3-borotropic shift would have a weaker driving force for rearomatisation.



Scheme 45. Proposed cyclopropyl naphthyl boronate complex **161** that may undergo dearomative 1,2-metallate rearrangement/ring opening.

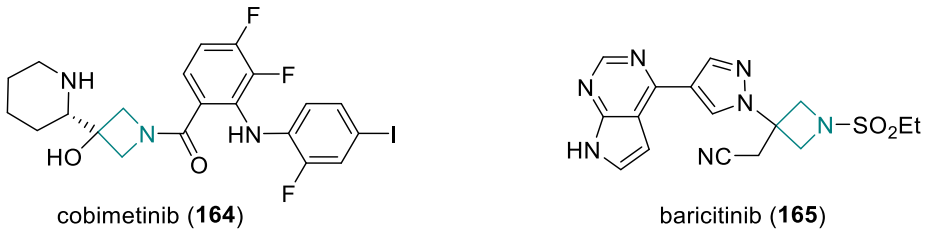
3. Synthesis of azetidines *via* azabicyclobutyl boronate complexes

3.1. Azetidines and azabicyclo[1.1.0]butane

3.1.1. Azetidines in drug molecules

In 2014, Njardarson and co-workers analysed a database of all U.S. FDA approved drug molecules and found that small-molecule drugs on average comprised 2.3 nitrogen atoms per drug.[101] Two of the most commonly encountered nitrogen containing motifs were the saturated heterocycles piperidine and pyrrolidine while the saturated four-membered heterocycle, azetidine, was reported to be much less common.[101] However, the azetidine motif exhibits greater metabolic stability than the larger ring analogues[102] and the structural rigidity of the strained ring can impart three-dimensionality into potential drug molecules while also increasing bioavailability.[103–105]

Therefore, new methods that enable the synthesis of functionalised azetidines are desirable due to the expected increase in demand for azetidines in drug targets. Indeed, since the report by Njardarson and co-workers, azetidine-containing drug molecules cobimetinib[46] (melanoma with BRAF mutation treatment) and baricitinib[47] (rheumatoid arthritis treatment) have both been FDA approved (Figure 6).



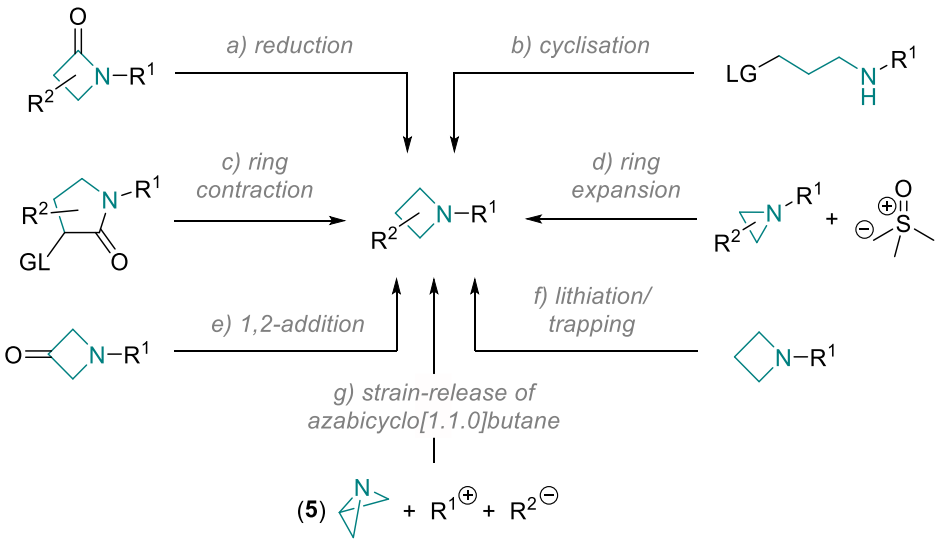
cobimetinib (**164**) baricitinib (**165**)

Figure 6. Recently FDA approved drug molecules containing an azetidine ring.

3.1.2. Synthesis of azetidines

A selection of general methods for the synthesis of substituted azetidines is outlined in Scheme 46. The reduction of readily available β-lactams[106] and the intermolecular cyclisation of amines[107] are common methods particularly for the synthesis of C2-substituted azetidines

(Scheme 46a,b). Alternatively, azetidines can be constructed from other ring sizes, for example, ring contraction from γ-lactams[108] or ring expansion from aziridines (Scheme 46c,d).[109]



Scheme 46. Methods for the synthesis of substituted azetidines.

Another approach to substituted azetidines is to functionalise an existing azetidine ring. Therin, the coupling of azetidines with other fragments, for example, nucleophilic 1,2-addition to 3-azetidinones[46] or lithiation followed by electrophilic trapping in the 2-position of azetidines[110] allows for an increase of molecular complexity (Scheme 46e,f).

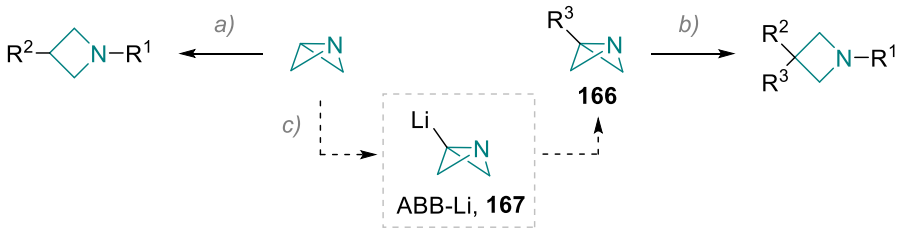
As discussed in section 1.2.3, recent developments have demonstrated that the highly strained azabicyclo[1.1.0]butane (ABB, **5**) is an effective synthon for 1,3-substituted azetidines (Scheme 46g).[51] The bridgehead carbon of azabicyclo[1.1.0]butane is electrophilic so prone to nucleophilic attack which opens the strained bicyclic structure to give the azetidine skeleton. ABB is also easily accessible in two steps from cheap and readily available allyl amine (see Scheme 7b).

3.1.3. Lithiation–borylation of azabicyclo[1.1.0]butane

While ABB has been shown as an effective building block in the synthesis of 1,3-substituted azetidines (Scheme 47a), the ability to access 1,3,3-trisubstituted azetidines through a strain-release strategy is more difficult. The 1,3-functionalisation of azabicyclo[1.1.0]butanes which already have a substituent at C3 has been described (Scheme 47b).[40,52,111,112] However, unlike ABB, to access molecules such as **166** requires lengthy synthetic routes.

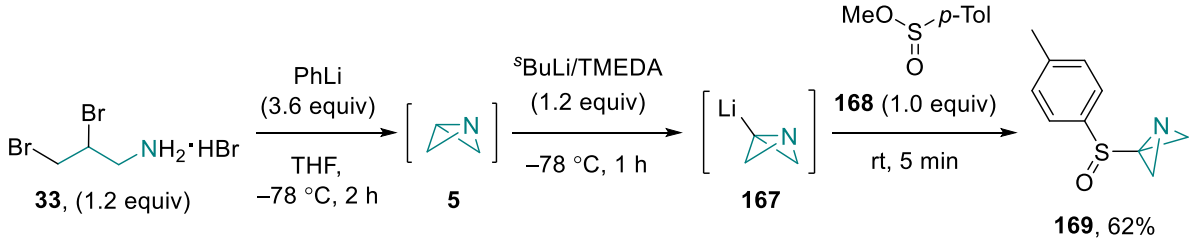
It was proposed by the Aggarwal group that ABB could in fact also act as a synthon for 1,3,3-trisubstituted azetidines by the direct substitution of ABB at C3 (Scheme 47c). Due to

the high ring strain of ABB, this methodology takes advantage of the acidity of the bridgehead C–H bond to access ABB-lithium (ABB-Li, **167**). This is a polarity reversal approach as ABB-Li is nucleophilic at C3 rather than electrophilic. After nucleophilic addition to introduce a substituent at C3, strain-release 1,3-functionalisation can occur to give the desired 1,3,3-trisubstituted azetidine.



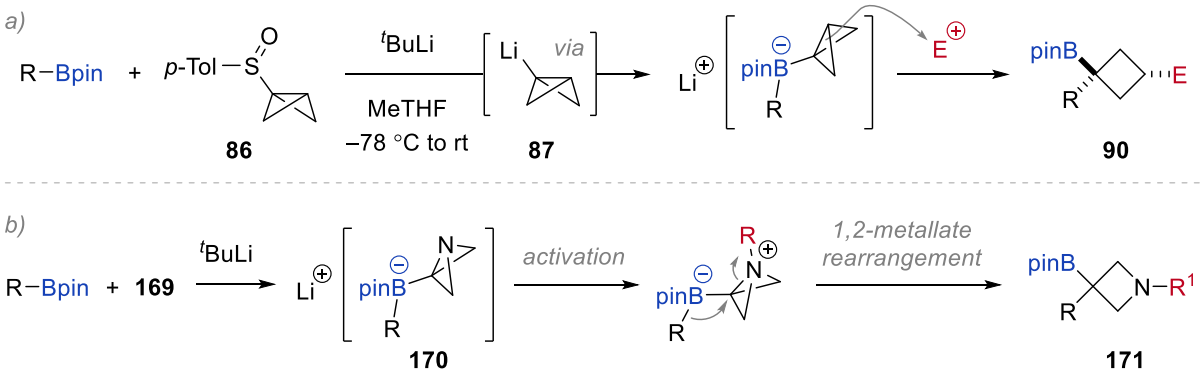
Scheme 47. Strain-release synthetic routes to substituted azetidines.

It was demonstrated that after the *in situ* generation of ABB from ammonium salt **33**, ABB could indeed be lithiated selectively at C3 using *sec*-butyllithium ligated by tetramethylethylenediamine (TMEDA, Scheme 48).[113] This gave ABB-Li which could be trapped by sulfinate **168** to give sulfoxide **169** in 62% overall yield.



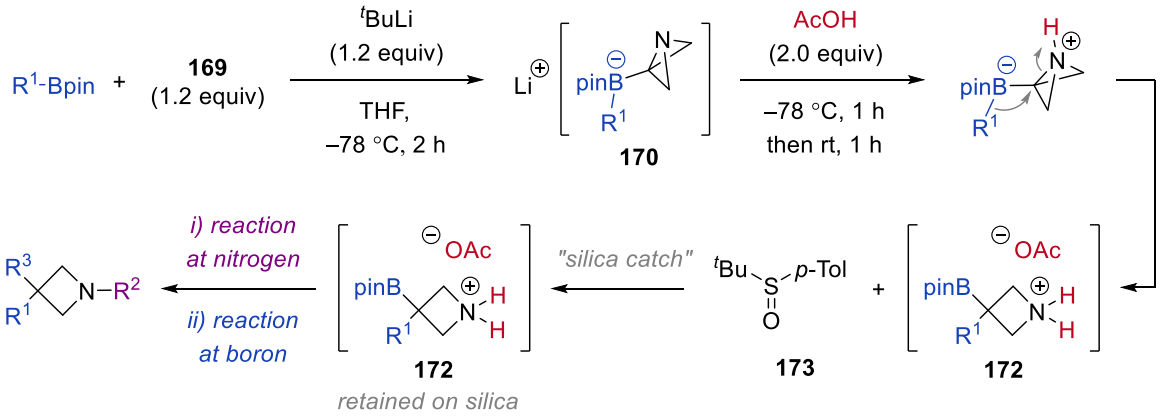
Scheme 48. Lithiation of azabicyclo[1.1.0]butane and trapping as a sulfoxide.

The use of sulfoxide **169** to access 1,3,3-trisubstituted azetidines was then investigated.[113] Reminiscent of the homologation of boronic esters with BCB-Li, (shown again in Scheme 49a), it was proposed that sulfoxide **169** could undergo lithium-sulfoxide exchange to regenerate ABB-Li. In the presence of a boronic ester this would lead to the formation of strained boronate complex **170** (Scheme 49b). The activation of the nitrogen lone pair of **170** would result in a strain-release 1,2-metallate rearrangement to give 1,3,3-trisubstituted azetidine **171** with the boronic ester functional group retained.



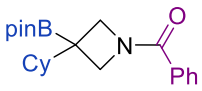
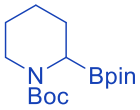
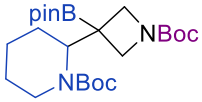
Scheme 49. Analogous reactions involving the homologation of boronic esters with a four-membered ring.

As anticipated, the addition of *tert*-butyllithium to a mixture of sulfoxide **169** and a boronic ester resulted in complete boronate formation.[113] It was found that the optimum activation conditions were the treatment of boronate **170** with 2.0 equivalents of acetic acid. This triggered the desired 1,2-metallate rearrangement to give azetidinium salt **172** (Scheme 50). The by-product from sulfoxide-lithium exchange (**173**) was removed by a "silica catch" purification, whereby **172** is retained on silica while **173** is eluted with ethyl acetate. The azetidinium salt retained on silica was shown to be a versatile intermediate, as the azetidine nitrogen could then be further functionalised. For example, with cyclohexyl pinacol boronic ester, the azetidine salt could be Boc protected to give azetidine **174** in good yield (Table 4, entry 1). Alternatively, subjecting the azetidine salt to amide coupling conditions with benzoic acid, amide coupling reagent HATU and *N*,*N*-diisopropylethylamine (DIPEA) gave azetidine **175** (entry 2).



Scheme 50. Lithiation–borylation of azabicyclo[1.1.0]butane to give 1,3,3-trisubstituted azetidines and further diversification through reaction at nitrogen or boron.

Table 4. Selected examples of azetidines accessible through the lithiation–borylation of azabicyclo[1.1.0]butane.

entry	boronic ester	conditions i)	conditions ii)	product	yield
1	Cy–Bpin	Boc_2O, NEt_3	none		**174**, 80%
2	Cy–Bpin	PhCOOH, $^{i}Pr_2NEt$, HATU	none		**175**, 70%
3	Cy–Bpin	Boc_2O, NEt_3	H_2O_2/NaOH		**176**, 70%
4		Boc_2O, NEt_3	none		**177**, 54%

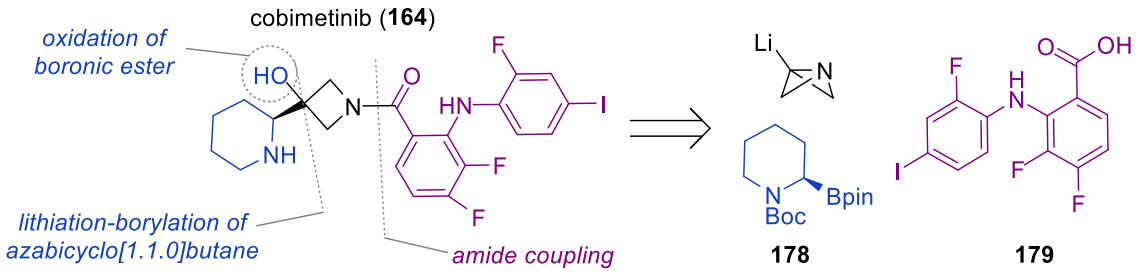
An advantage of this method relative to other procedures for the synthesis of azetidines is that the azetidine product contains a boronic ester substituent that can be further diversified. For example, alcohol **176** could be obtained by the oxidation of boronic ester **174** and was isolated in 70% over two steps from cyclohexyl pinacol boronic ester (entry 3). A scope of 27 different boronic esters was demonstrated which included primary, secondary, tertiary, vinyl and aryl boronic esters.[113] A significant example was a piperidine derived boronic ester, giving azetidine **177** in 54% yield (entry 4). Alkyl groups with α-heteroatoms are known to migrate slowly[114] however, the strain-release of the azabicyclo[1.1.0]butane motif is a sufficiently large driving force for 1,2-metallate rearrangement.

3.2. Project proposal

3.2.1. Project outline

The lithiation–borylation of ABB is a rapid, modular approach to the synthesis of 1,3,3-trisubstituted azetidines. It was proposed that one specific azetidine drug molecule, cobimetinib, would be easily accessible by this method from simple building blocks: ABB-Li, boronic ester **178** and benzoic acid **179** (Scheme 51).

The synthesis of cobimetinib using ABB is summarised in this chapter and this work is also outlined in the following publication: A. Fawcett, A. Murtaza, C. H. U. Gregson, V. K. Aggarwal, *J. Am. Chem. Soc.*, **2019**, *141*, 4573–4578.[113] The contribution of other authors to this publication is already outlined in section 3.1.3.

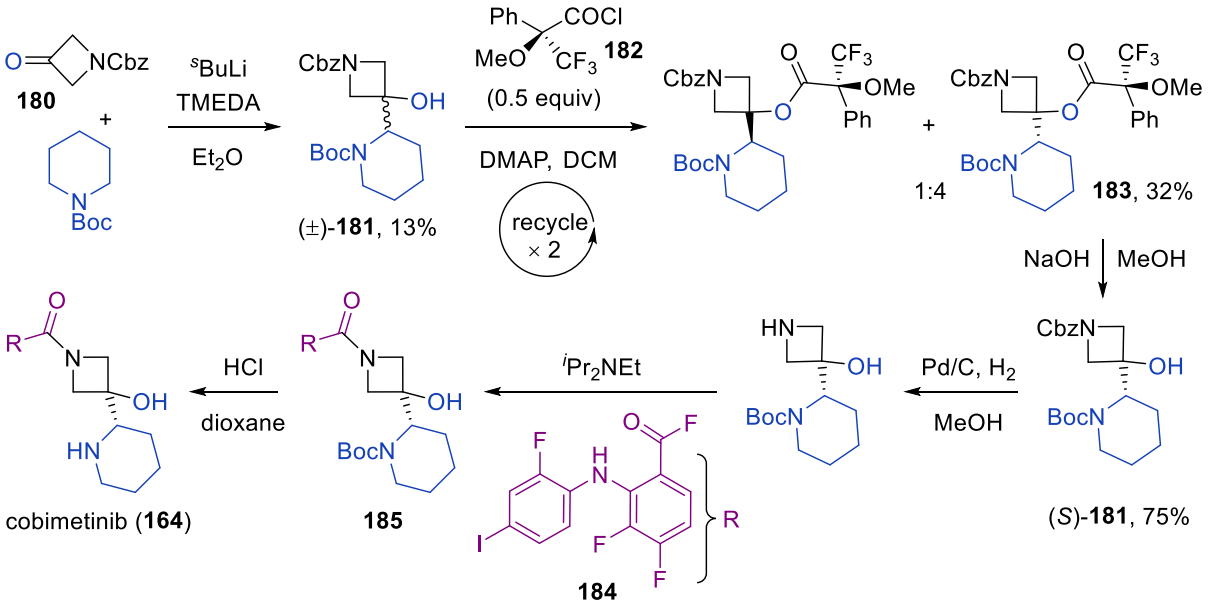


Scheme 51. Proposed synthetic route to cobimetinib.

3.2.2. Previous syntheses of cobimetinib

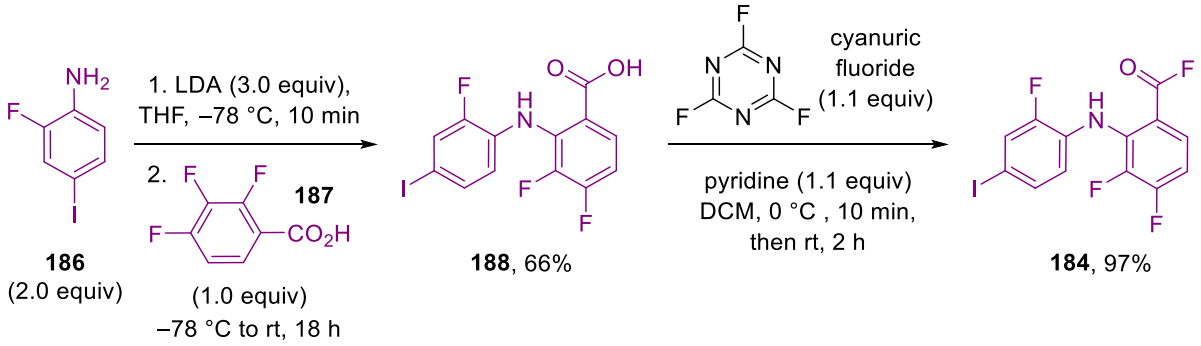
Cobimetinib was first prepared by Rice and co-workers and identified as an effective MEK inhibitor.[46] MEK inhibitors affect the MAPK/ERK pathway, a protein signalling pathway which is overactive in certain cancers.[115] Cobimetinib has since been FDA approved for the treatment of advanced melanoma with BRAF mutation in combination with vemurafenib, a BRAF inhibitor.[116]

The synthesis of cobimetinib by Rice and co-workers is outlined in Scheme 52.[46] The first step is a low yielding 1,2-addition of (*N*-Boc-piperidin-2-yl)lithium to azetidinone **180** to give racemic azetidine **181**. The resolution of this species was achieved by esterification with acyl chloride **182** to give major diastereomer **183** which was isolated by chromatography and hydrolysed to give optically pure (*S*)-**181**. Selective deprotection of the azetidine followed by amide coupling with acyl fluoride **184** gave azetidine **185**, which was Boc deprotected with HCl/dioxane to give cobimetinib.



Scheme 52. First reported synthesis of cobimetinib.

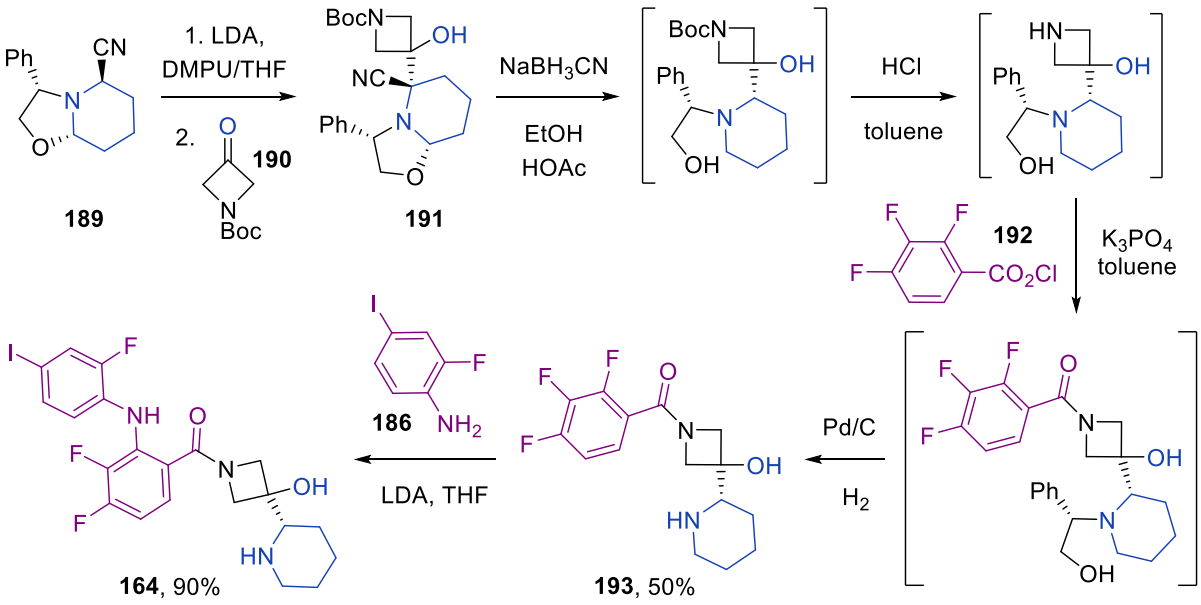
Acyl fluoride **184** was synthesised by the regioselective S_NAr reaction between aniline **186** and 2,3,4-trifluorobenzoic acid (**187**) to give benzoic acid **188**, followed by fluorination with cyanuric fluoride (Scheme 53).[46]



Scheme 53. Synthesis of 3,4-difluoro-2-((2-fluoro-4-iodophenyl)amino)benzoyl fluoride.

An alternative manufacturing route to cobimetinib has been reported starting from compound **189**, itself derived from the chiral pool (Scheme 54).[117,118] As before, the first step is a 1,2-addition to azetidinone **190** to give **191** in an unspecified dr and yield. The next three steps are performed without intermediate purification to access azetidine **193** in 50% yield. Specifically, these steps involve a reductive decyanation and C–O bond cleavage, followed by Boc deprotection and amide bond formation with 2,3,4-trifluorobenzoyl chloride (**192**).

Finally, the S_NAr reaction with aniline **186** affords cobimetinib. The advantage of this method is the reduced number of purification steps and the use of hemiaminal **189** as the starting material for which the manufacturing route is already established.[119]



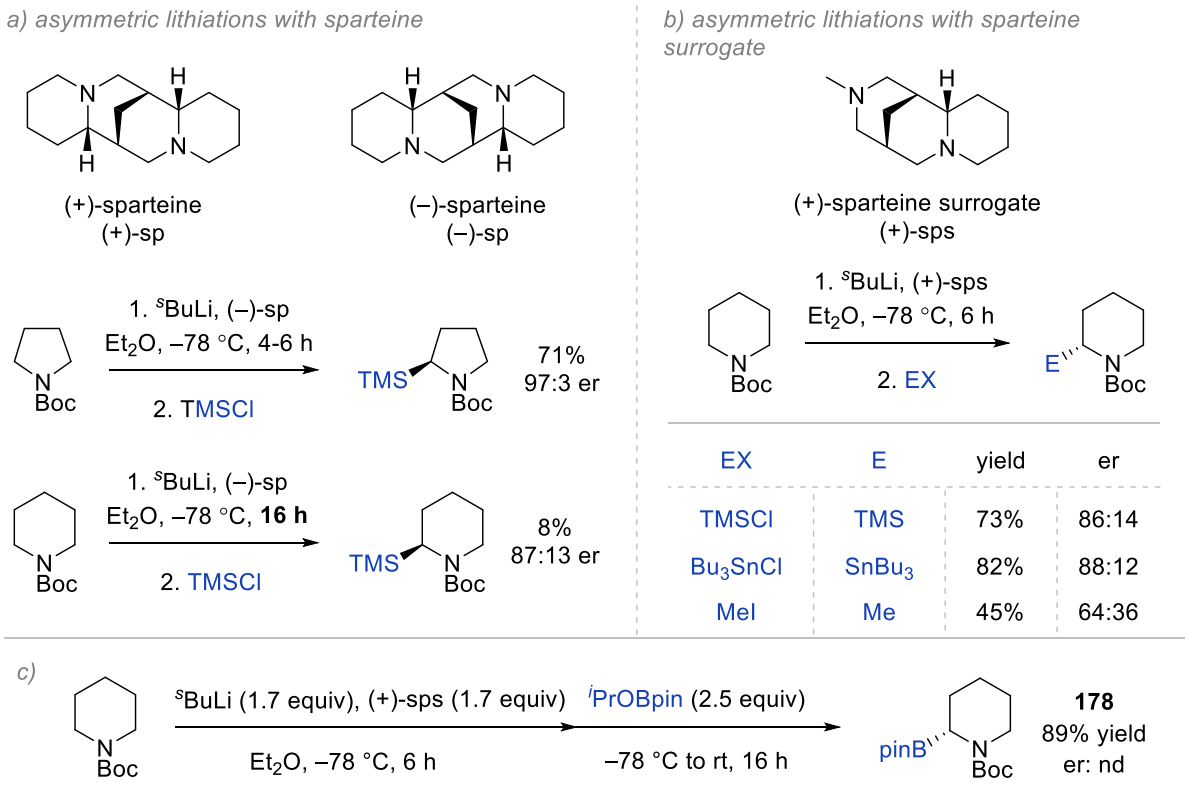
Scheme 54. Manufacturing route to cobimetinib.

3.3. Results and discussion

3.3.1. Piperidine boronic ester synthesis

The first objective was to synthesise piperidine boronic ester **178** in enantioenriched form. Beak and co-workers reported that while the lithiation of *N*-Boc-pyrrolidine with *sec*-butyllithium and (–)-sparteine proceeded in good yield with high enantioselectivity, the equivalent reaction with *N*-Boc-piperidine was low yielding and much poorer enantioselectivity was achieved (Scheme 55a).[120,121]

An improvement was reported by O'Brien and co-workers which is the asymmetric deprotonation of *N*-Boc-piperidine with (+)-sparteine surrogate (Scheme 55b).[122] The less hindered amine ligand enhances the reactivity of *sec*-butyllithium, so much faster lithiation of *N*-Boc-piperidine occurred and enantioinduction up to 88:12 er was possible. Fortunately, the major enantiomer using (+)-sparteine surrogate has the same stereochemistry as that found in cobimetinib.



Scheme 55. Asymmetric deprotonation of *N*-Boc-piperidine and *N*-Boc-pyrrolidine.

This methodology was applied to the synthesis of boronic ester **178**. Lithiation of *N*-Boc-piperidine with *sec*-butyllithium/(+)-sparteine surrogate followed by trapping with *iso*-propoxy pinacol borate gave **178** in 89% yield. At this stage, the er of **178** was unknown,

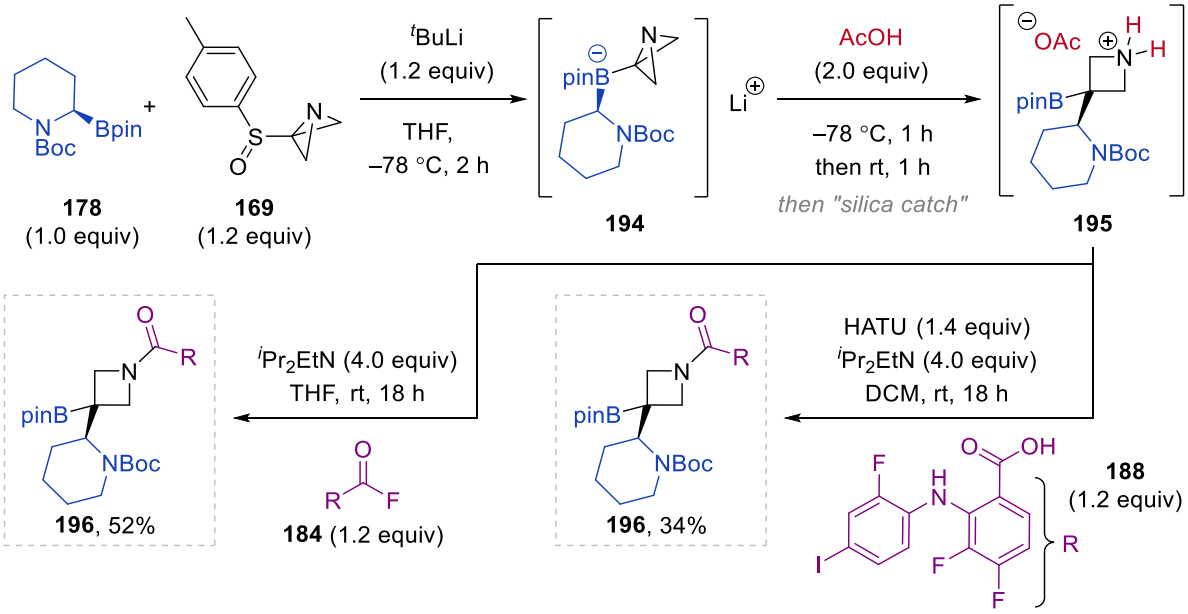
however, *iso*-propoxy pinacol borate has been used previously to trap enantioenriched organolithium species in high enantioexcess.[114]

3.3.2. Synthesis of cobimetinib

A solution of boronic ester **178** and sulfoxide **169** in THF was treated with *tert*-butyllithium to form boronate complex **194** (Scheme 56). After the addition of acetic acid and "silica catch" purification, salt **195** and the top layer of the silica gel plug were then collected and subjected to amide coupling conditions with benzoic acid **188**, HATU and DIPEA. This gave desired boronic ester **196** in 34% yield (Scheme 56).

The homologation step to give salt **195** is known to achieve 54% yield after Boc protection[113] so it was deduced that the amide coupling was not proceeding in very high yield. Indeed, a control amide coupling reaction of azetidine hydrogen chloride with benzoic acid **188** under the same conditions gave the product in only 70% yield. When the homologation and amide coupling are then telescoped, a moderate yield of 34% is to be expected.

However, the amide coupling conditions used by Rice and co-workers,[46] which utilised acyl fluoride **184**, gave boronic ester **196** in 52% yield (Scheme 56).

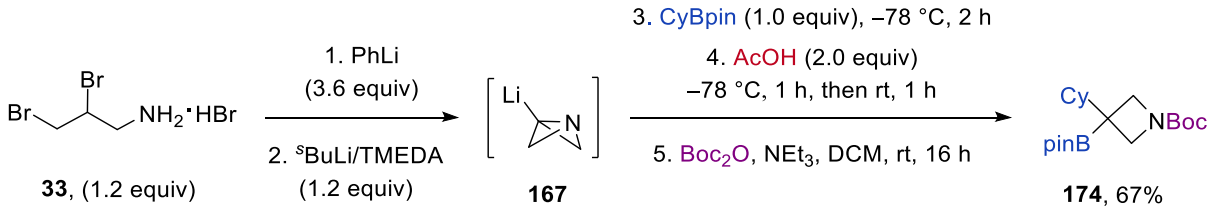


Scheme 56. Reaction of piperidine derived boronic ester and azabicyclobutyl sulfoxide followed by amide coupling.

Up to this point, investigations into the lithiation–borylation of ABB had only been performed *via* sulfoxide **169**. The reason for this is that **169** can be purified and is a bench stable solid reagent. Therefore, when performing reactions using ABB-Li, much more control over

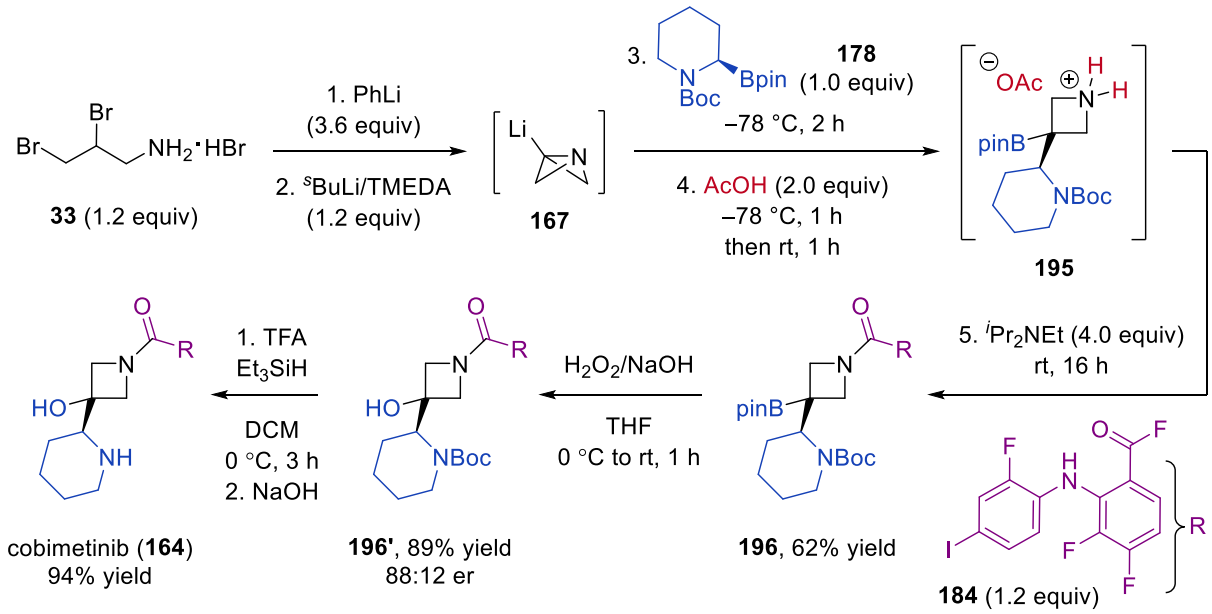
equivalents and potential impurities can be achieved if ABB-Li is generated from sulfoxide **169**. In addition, the synthesis of **169** has been scaled to 1.7 g (8.8 mmol) so if many different azetidines are required, the reaction *via* the sulfoxide is more time efficient.[113]

However, if only one particular azetidine is required, the reaction *via* sulfoxide **169** is less efficient, both in terms of time and atom economy. A "one-pot" procedure was established, whereby ABB was formed, lithiated and borylated *in situ* with cyclohexyl pinacol boronic ester (Scheme 57). The activation of the boronate complex with acetic acid followed by Boc protection afforded desired azetidine product **174** in 67% yield. One advantage of this method is that "silica-catch" purification is not required, as no problematic sulfoxide by-products are present.



Scheme 57. One pot procedure for the lithiation–borylation of azabicyclo[1.1.0]butane.

This procedure was applied to the synthesis of cobimetinib (Scheme 58). In this case, starting from ammonium salt **33**, the synthesis of boronic ester **196** was achieved in an enhanced yield of 62%.



Scheme 58. Synthesis of cobimetinib by lithiation–borylation of azabicyclo[1.1.0]butane.

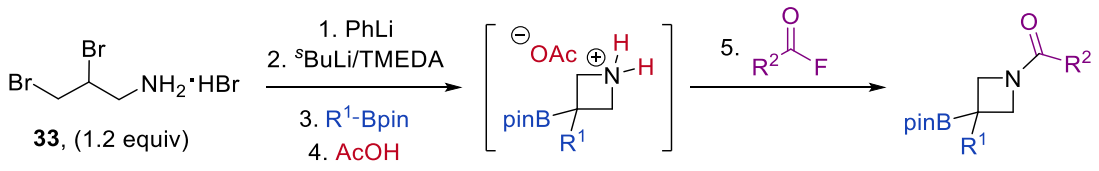
Enantiospecific oxidation of the boronic ester with hydrogen peroxide/sodium hydroxide proceeded in 89% yield to give alcohol **196'**. This is not a high yield for this often-quantitative reaction, however, a tertiary boronic ester is a more difficult substrate to oxidise due to steric hindrance. The enantiomeric ratio of alcohol **196'** was found to be 88:12 er which is the maximum O'Brien and co-workers observed for the asymmetric lithiation of *N*-Boc piperidine.[122] Finally, Boc deprotection with trifluoroacetic acid (TFA)/triethyl silane followed by neutralisation with sodium hydroxide solution gave cobimetinib (**164**) in 94% yield.

This process transforms piperidine boronic ester **178** into cobimetinib in an overall yield of 52%. This is an improvement on the manufacturing route to cobimetinib with similar step economy.[117]

3.3.3. Conclusions and future work

A new route to the anti-cancer drug cobimetinib has been established that employs azabicyclo[1.1.0]butane as a synthon for a 1,3,3-trisubstituted azetidine. The synthesis applies methodology that was previously investigated within the Aggarwal research group, namely the lithiation–borylation of azabicyclo[1.1.0]butane.[113] The synthesis of cobimetinib was achieved in three steps, one of which is a telescoped process that transforms amine salt **33**, piperidine boronic ester **178** and acyl fluoride **184** into an advanced intermediate in one pot with a yield of 62%.

While it is unlikely that the synthesis of cobimetinib *via* ABB will replace the established route, due to the requirement for (+)-sparteine surrogate and the moderate enantioselectivity, this synthesis has demonstrated the applicability of this methodology to the synthesis of biologically active azetidines. In addition, this approach is modular, so by choosing a different boronic ester, acyl fluoride or boronic ester transformation, a variety of chemical analogues could be synthesised in short succession. Therefore, future work in this area could be the synthesis of a library of azetidines that could be analysed for bioactivity (Scheme 59). Furthermore, as the procedure is general, the library synthesis could be translated to an automated synthesis platform to enhance efficiency.[123]



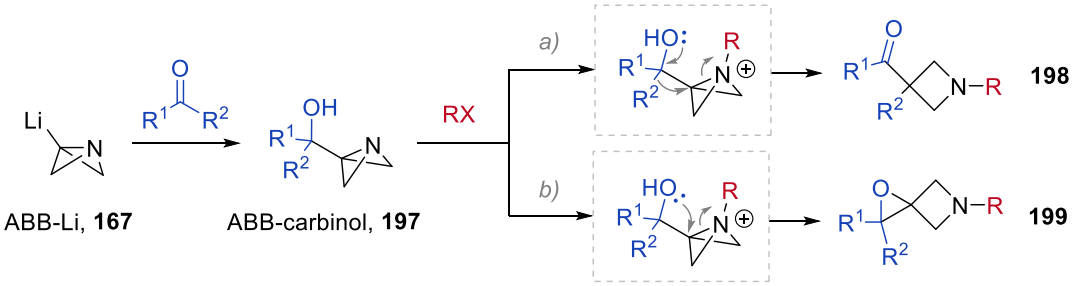
Scheme 59. Possible synthesis of a library of azetidines.

4. Strain-release reactions of azabicyclo[1.1.0]butyl carbinols

4.1. Project proposal

Following the successful use of ABB-Li as a synthon for 1,3,3-trisubstituted azetidines, alternative electrophiles that could also participate in subsequent strain-release chemistry were investigated. Due to a diverse and accessible feedstock of ketones and aldehydes, their reaction with ABB-Li was explored.

It was envisioned that a 1,2-addition of ABB-Li at the carbonyl carbon would occur to give an alcohol with the ABB group in the β-position (ABB carbinol **197**, Scheme 60). Following activation of the ABB nitrogen lone pair, **197** could rearrange one of two ways. Firstly, after activation, a semipinacol rearrangement could take place with migration of one alcohol substituent to give keto azetidine **198** with an all-carbon quaternary centre. Alternatively, the oxygen lone pair could engage the strained ABB central bond through a spirocyclisation S_N2 pathway to give spiroepoxy azetidine **199**.



Scheme 60. Proposed synthesis of ABB-carbinols and their subsequent reactivity.

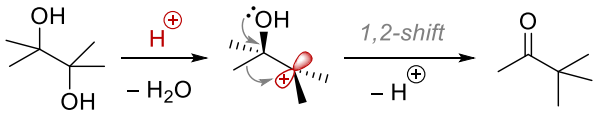
The investigation into these two reaction pathways is summarised in this chapter and this work is also outlined in the following publication: C. H. U. Gregson, A. Noble, V. K. Aggarwal, *Angew. Chem. Int. Ed.*, **2021**, *60*, 7360–7365.[124]

4.2. The semipinacol rearrangement reaction

4.2.1. General introduction to the semipinacol rearrangement reaction

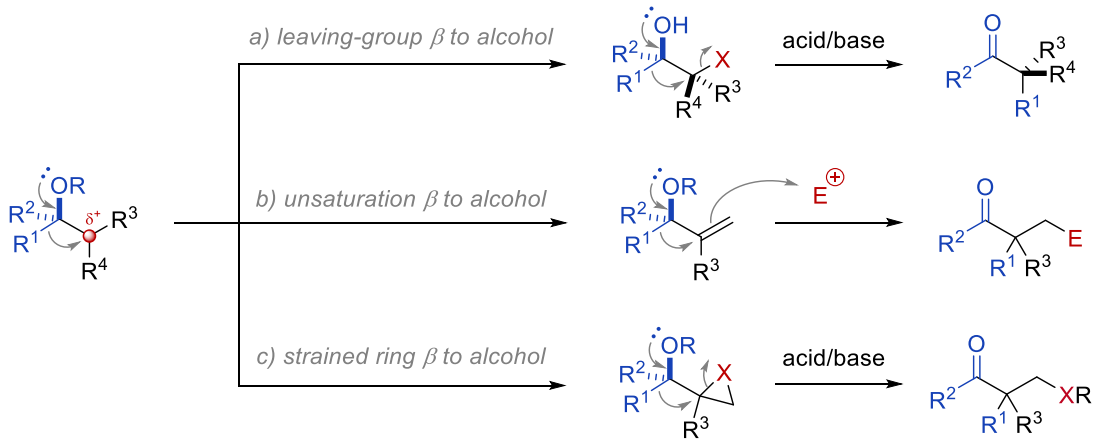
The pinacol rearrangement refers to the acid catalysed reaction of a vicinal diol to give a ketone through loss of water and a 1,2-alkyl shift. The primary example is the conversion of pinacol to pinacolone (Scheme 61) which was first reported in 1859, although the correct reaction product was not elucidated until 1873.[125] The reaction involves the acid activation of one of the hydroxyl groups followed by the loss of water to give a carbocation. One of the adjacent

methyl groups can migrate to the electrophilic carbon with concomitant stabilisation by the other hydroxyl lone pair to give the ketone product.



Scheme 61. Pinacol rearrangement.

An extension to the pinacol rearrangement reaction is known as the semipinacol rearrangement reaction which involves a 1,2-shift to an electrophilic carbon centre, β to a hydroxyl group, which has been generated by other means. In the semipinacol rearrangement, the electrophilic centre can be generated by the loss of a leaving group (Scheme 62a), electrophilic activation of an allylic alcohol (Scheme 62b) or the cleavage of a strained ring among other methods (Scheme 62c). The semipinacol rearrangement has been demonstrated as an efficient method for the construction of hindered quaternary centres and spirocycles. For this reason, it is often used in the total synthesis of complex natural products.[126]



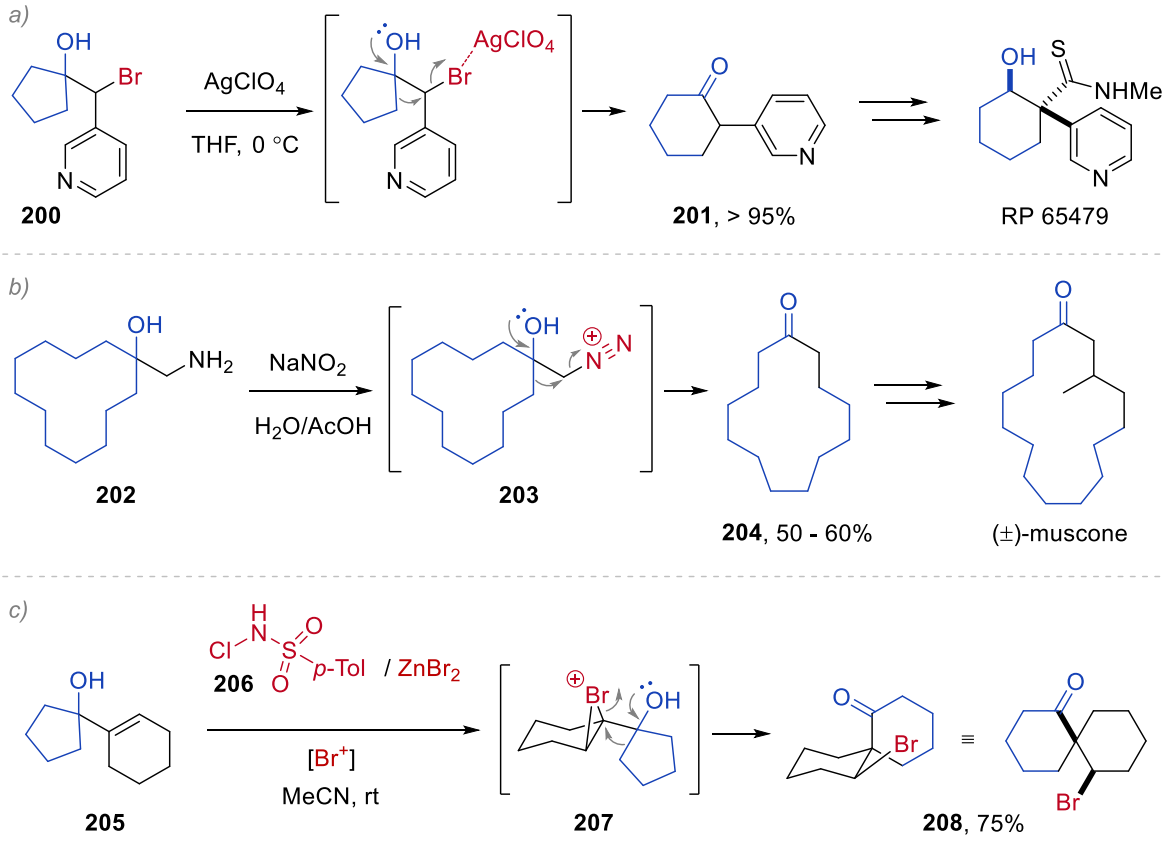
Scheme 62. Classes of semipinacol rearrangement reactions.

An example of a leaving group-driven semipinacol rearrangement is the rearrangement of bromohydrin **200** (Scheme 63a).[127] The addition of silver perchlorate activates the bromide which induces a ring expansion semipinacol rearrangement to give cyclohexanone **201**. This species was used as a precursor to natural product RP 65479 by Hart and co-workers.

Another commonly used leaving group in the semipinacol rearrangement is N_2 from a highly reactive 1,2-hydroxyl diazonium intermediate such as **203** (Scheme 63b).[128] This process is known as the Tiffeneau-Demjanov rearrangement[129] and involves the diazotisation of 1,2-amino alcohols to give rearranged ketone products. For example, amino alcohol **202** was transformed into ketone **204** in Nagel's total synthesis of (±)-muscone. Another approach to

the Tiffeneau-Demjanov rearrangement is the direct diazotisation of ketones by the addition of a diazoalkane. This generates the α-hydroxy diazonium intermediate which can undergo the 1,2-rearrangement to give a ketone homologated by one methylene unit.[129]

Allylic alcohols can undergo a semipinacol rearrangement if reacted with a suitably electrophilic activating agent. For example, a mixture of chloroamide **206** and zinc bromide in the presence of allylic alcohol **205** leads to the formation of bromonium intermediate **207** through the addition of "Br^+" across the double bond (Scheme 63c).[130] This species undergoes a semipinacol rearrangement to give spirocyclic ketone **208**. The process is diastereoselective as the alkyl migration occurs through an S_N2-type mechanism.

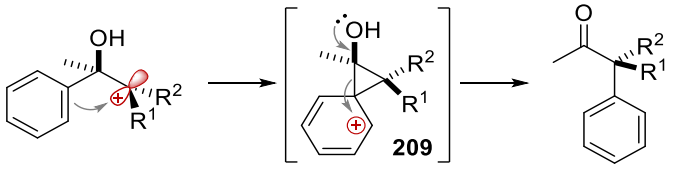


Scheme 63. Examples of semipinacol rearrangement reactions: a) halide as a leaving group, b) N_2 as a leaving group and c) allylic alcohol rearrangement induced by a halonium ion.

The above-mentioned examples all involve the rearrangement of a symmetric alcohol with no choice of migrating group. With asymmetric alcohols, the choice of migrating group is governed by a combination of effects: the migratory aptitude of the alcohol substituents and the conformation/configuration of the reactive intermediate. While migratory aptitude is associated with the specific functional group, the conformation/configuration of the reactive

intermediate is system-specific, as is the extent to which migratory aptitude influences selectivity.

Migratory aptitude in the semipinacol rearrangement generally follows the trend aryl > alkenyl > hydride > substituted alkyl > less substituted alkyl.[131] This sequence represents the extent to which each group is able to stabilize the β-carbocation. The superior migratory aptitude of aryl groups is due to the ability of the π system to engage the β-carbocation to form stabilised phenonium ion intermediate **209**, which facilitates the semipinacol rearrangement (Scheme 64).



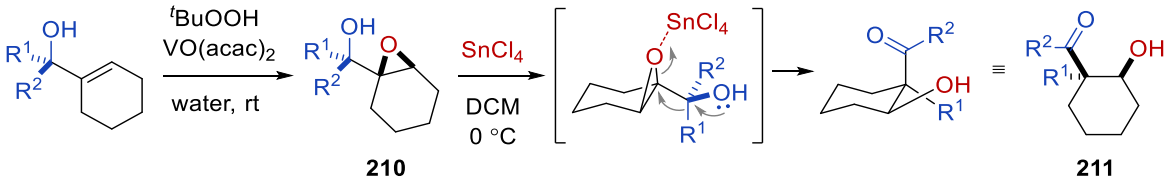
Scheme 64. Semipinacol migration of a phenyl group through a stabilised intermediate.

Despite secondary alkyl groups having a greater migratory aptitude than primary, the Tiffeneau-Demjanov rearrangement is known to generally proceed by the preferential migration of the least hindered (least substituted) alkyl group. This is because the Tiffeneau-Demjanov rearrangement proceeds under steric control and so the favoured conformation of the intermediate has the dominating effect on selectivity.

As the effect of migratory aptitude on selectivity is system-specific, a more detailed look into reaction selectivity will be made on systems most similar to the one proposed. Therefore, examples of semipinacol rearrangements driven by the cleavage of a strained ring are discussed in greater detail below.

4.2.2. Semipinacol rearrangements triggered by the cleavage of a strained ring

The proposed rearrangement of ABB-carbinols bears a resemblance to the semipinacol rearrangement of α-hydroxy epoxides.[132] Marson and co-workers demonstrated that cyclohexyl α-hydroxy epoxides such as **210** could undergo a semipinacol rearrangement in the presence of tin tetrachloride (Scheme 65).[133] The Lewis acid activates the epoxide which triggers a 1,2-shift to give hydroxy ketone **211**. The rearrangement is stereospecific as the epoxide ring opening proceeds in an S_N2-type manner, which delivers the migrating group to the opposite side of the ring to the hydroxyl group in the product.



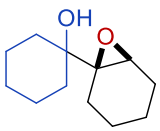
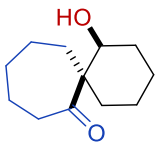
Scheme 65. Semipinacol rearrangement of cyclohexyl α-hydroxy epoxides.

Marson and co-workers went on to evaluate the selectivity of the migration of different substituents when performing their reaction scope (Table 5).[133] They showed that while methyl does migrate when no other groups are available (entry 1), the selectivity for methyl migration is lower than any of the other groups screened. High selectivity for the migration of primary alkyl, cyclopropyl, tertiary butyl, vinyl and phenyl groups over methyl were shown to occur (entries 2-6). In addition, vinyl and phenyl groups were shown to migrate preferentially over a primary benzylic group (entries 7-8). The ring expansion of hydroxy epoxide **212** to give 7-membered ring containing product **213** was also achieved using this procedure.

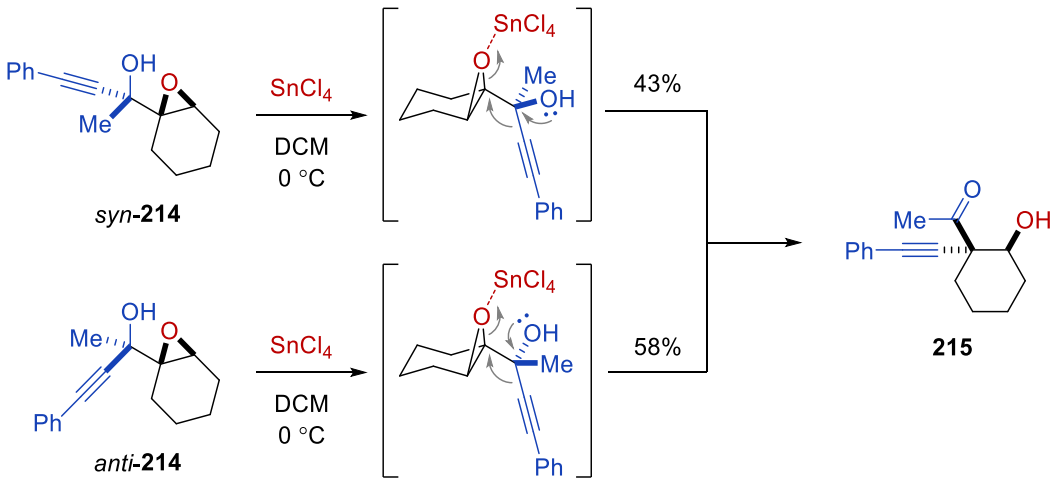
Table 5. Substrate scope for the semipinacol rearrangement of cyclohexyl α-hydroxy epoxides.

entry	R^1	R^2	yield of **211**
1	Me	Me	56%
2		Me	78%
3		Me	88%
4	^{t}Bu	Me	75%
5		Me	95%
6	Ph	Me	99%

entry	R^1	R^2	yield of **211**
7			73%
8	Ph		84%

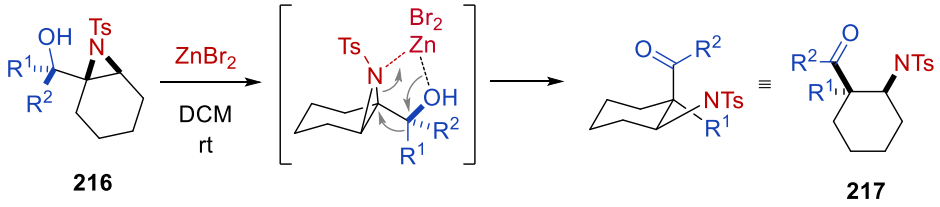
	reactant	product	yield
9	 **212**	 **213**	41%

The authors show that the migration of an alkynyl group is possible under their reaction conditions (Scheme 66).[133] This is noteworthy as alkynes are known to be poor migrating groups.[134] This is due to their sp-hybridisation and thus the high activation energy required to form the necessary 3-centre-2-electron transition state during migration.[131] In this example, the reaction of both diastereomers of **214** led to the formation of the same ketone **215**. This demonstrates that in this case, alcohol configuration does not play a role in reaction selectivity.



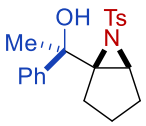
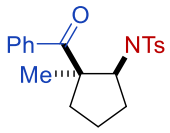
Scheme 66. Semipinacol rearrangements of diastereomeric alcohols **214** to give the same product.

Other structural analogues of ABB-carbinols are α-hydroxy aziridines **216** (Scheme 67). These species were shown by Tu and co-worders to undergo a strain-release semipinacol rearrangement in the presence of zinc bromide to give keto amines such as **217**.[135] When evaluating the reaction scope of asymmetric alcohols (Table 6), the authors saw that the reaction of **216** was highly selective over which substituent migrated, affording a single reaction product. In stark contrast to the previous example of α-hydroxy epoxides, it was found that the configuration of the starting material has the dominating effect on selectivity. The selective migration of ethyl over methyl was observed to give a methyl ketone product (entry 1), however, the opposite selectivity occurred with the other diastereomer of the starting material (entry 2). In this case, methyl migrated selectively over ethyl to give an ethyl ketone product despite the greater migratory aptitude of the ethyl group. It is reasoned that the Lewis acid coordinates to both the nitrogen of the aziridine and the alcohol oxygen, which locks the conformation of the starting material. As 1,2-migration happens concurrently with ring opening, whichever group is placed antiperiplanar to the cleaved C–N bond is the migrating group, regardless of migratory ability. Remarkably, this effect even allowed for the migration of the methyl group over phenyl in aziridine **218** to give phenyl ketone **219** in 85% yield (entry 4).

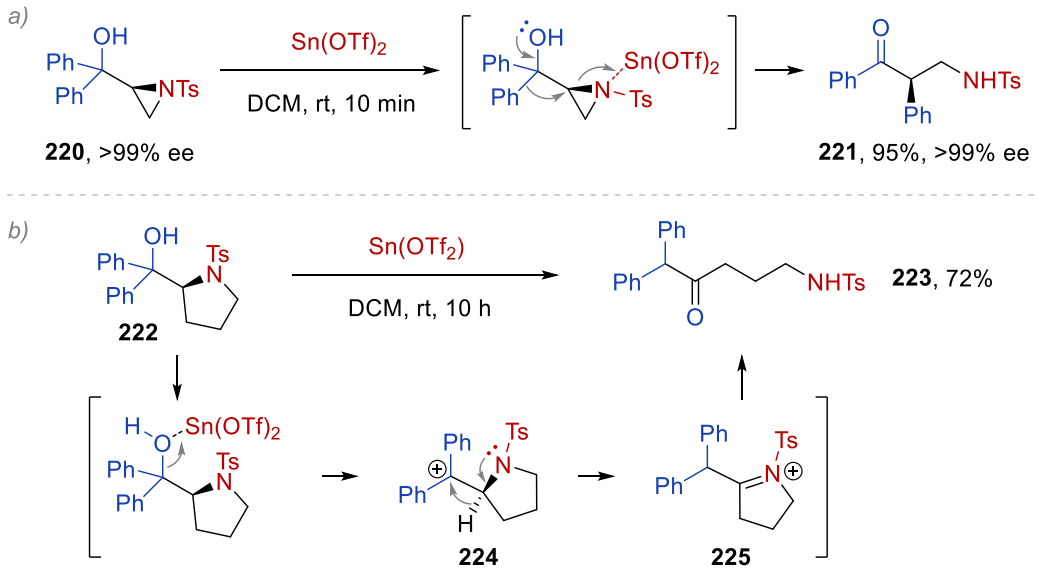


Scheme 67. Semipinacol rearrangement of cyclic α-hydroxy aziridines.

Table 6. Substrate scope for the semipinacol rearrangement of cyclic α-hydroxy aziridines.

entry	R^1	R^2	yield of **217**	entry	reactant	product	yield
1	Et	Me	89%	4	 **218**	 **219**	85%
2	Me	Et	90%				
3	Ph	H	85%				

A similar procedure was reported by Singh and co-workers who showed that α-hydroxy aziridine **220** underwent a semipinacol rearrangement when activated by tin triflate to give ketone **221** (Scheme 68a).[136] This reaction was demonstrated to be enantiospecific as no loss of ee was observed, so it must proceed through a stereospecific S_N2 inversion at the electrophilic carbon centre.



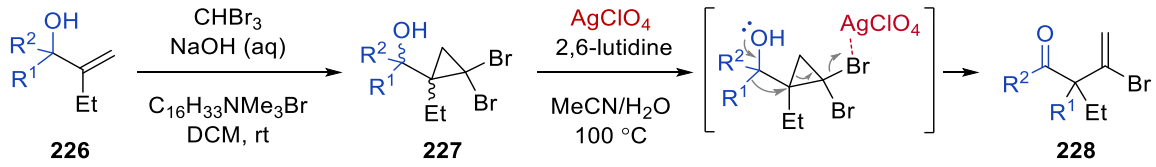
Scheme 68. Rearrangements of β-amino alcohols.

Interestingly, amino alcohol **222**, with a larger ring size, was shown to undergo an entirely different mechanism under the same reaction conditions (Scheme 68b). The addition of tin triflate led to the formation of **223** as the major reaction product. A plausible mechanism for the formation of **223** involves the initial Lewis acid activation of the alcohol lone pair rather than the amine lone pair to give carbocation **224**, which is stabilised by two phenyl groups. This species then undergoes an aza-semipinacol rearrangement with migration of hydride to give iminium ion **225** followed by hydrolysis to give ketone **223**.

The remarkable switch in mechanism when changing between substrates **220** and **222** that only differ in ring size shows the extent to which strain-release influences reactivity. The ring

opening of the aziridine ring in **220** is a much greater driving force than the ring opening of the pyrrolidine ring in **222**. Therefore, **220** has a better leaving group and a more electrophilic β hydroxy carbon than **222**. This is evidence that a semipinacol rearrangement mechanism is favoured over other pathways when a very labile leaving group is present. Furthermore, the strain-release of the C–N bond in **220** is facile as the semipinacol rearrangement is complete within 10 minutes at room temperature, whereas the cleavage of the C–N bond in **222** is much slower and required up to 10 hours to reach completion.[136]

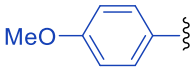
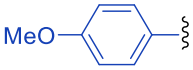
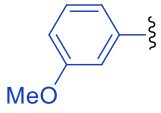
Yokoshima and co-workers have recently reported a semipinacol rearrangement reaction where the driving force is the cleavage of a cyclopropane ring (Scheme 69).[137] In their report, allylic alcohols **226** were first cyclopropanated with bromoform to afford a mixture of separable diastereomers of cyclopropyl carbinols **227**. Each diastereomer was subjected to a semipinacol rearrangement reaction facilitated by the addition of silver perchlorate. Similar to the reaction presented in Scheme 63a, the silver salt activates one of the bromide substituents, which induces cyclopropane ring opening and a semipinacol rearrangement. This results in the formation of β,γ-unsaturated ketone **228**.

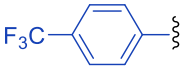


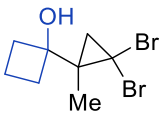
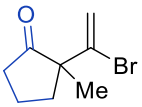
Scheme 69. Semipinacol rearrangement of cyclopropyl carbinols.

The authors show that the use of either diastereomer of **227** results in the formation of the same reaction product, confirming that configuration has no effect on selectivity in this system (Table 7). The migration of an electron rich *para*-methoxy phenyl group was found to be selective over methyl or hydride migration (entries 1 and 2). Whereas, when moving to the *meta*-methoxy substrate, lower reactivity was observed (entry 3). Furthermore, when an electron poor *para*-trifluoromethyl phenyl substrate was employed in the reaction, the selectivity was lost, and a complex mixture of products was obtained that could not be elucidated (entry 4). However, the ring expansion of cyclobutanol substrate **229** was also demonstrated to give ketone **230**, albeit in a moderate yield (entry 5).

Table 7. Substrate scope of the semipinacol rearrangement of cyclopropyl carbinols.

entry	R^1	R^2	yield of **228**
1		Me	72%[a] 68%[b]
2		H	84%[a] 70%[b]
3		H	28%[a] 21%[b]

entry	R^1	R^2	yield of **228**
4		H	nd[a] nd[b]

	reactant	product	yield
5	 **229**	 **230**	37%

[a] From the major diastereomer of **227**. [b] From the minor diastereomer of **227**.

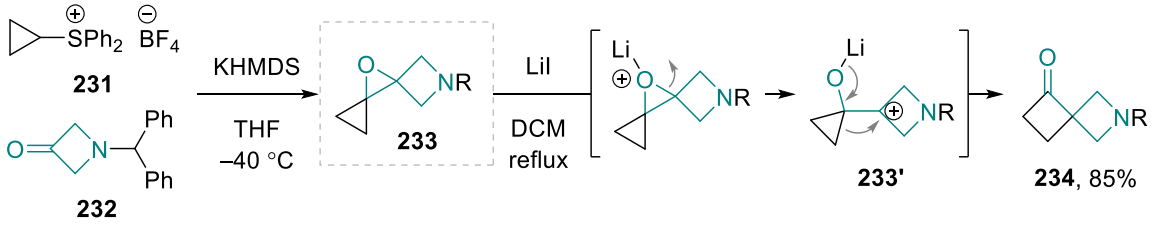
The examples discussed above demonstrate that the semipinacol rearrangement does not always proceed as expected. This is because relative rates of the desired process over competing processes and migratory group selectivity are dependent on a number of steric and electronic factors.

4.3. Spiroepoxy azetidines

The alternative reaction mechanism proposed leads to the formation of a spiroepoxy azetidine. Reported syntheses of such structures are few outside of the patent literature. This is surprising, as spirocycles containing the azetidine moiety are garnering increasing interest in medicinal chemistry applications.[43,138,139] Azetidines themselves are attractive targets due to their rigid, hydrophilic skeleton, and this rationale can be extended to spirocyclic azetidines.[140] Spirocycles also have desirable compact structures with well-defined conformations and exit vectors, while occupying a region of relatively unexplored chemical space.[141,142] Specifically, the formation of spiroepoxy azetidines would also be interesting as these structures are themselves highly strained and may display further interesting strain-release reactivity.[143]

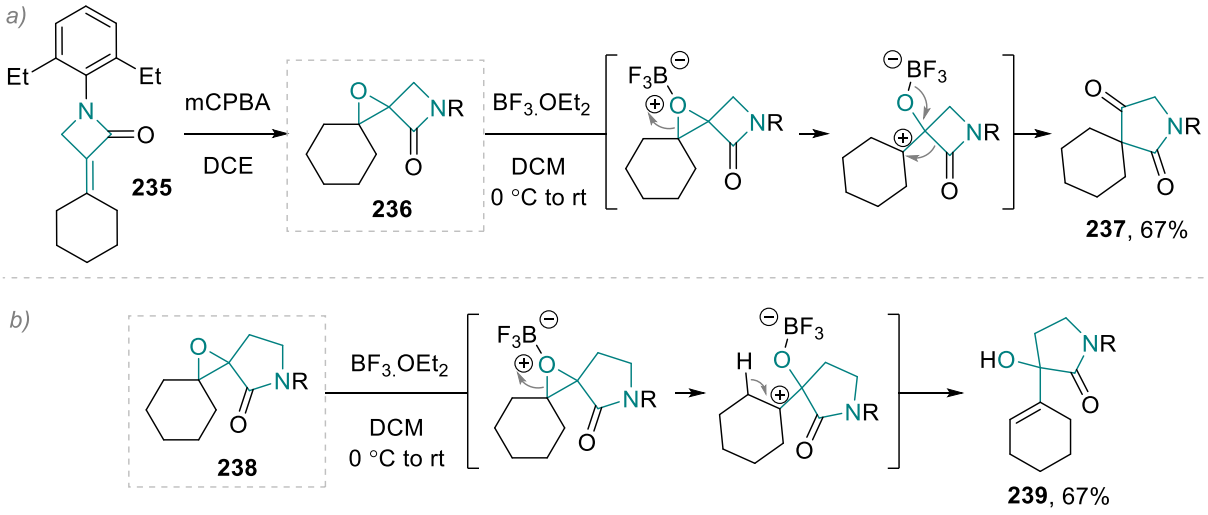
One example of the synthesis and reactivity of a spiroepoxy azetidine was reported by Carriera and co-workers (Scheme 70).[143] Sulfonium salt **231** was deprotonated with potassium bis(trimethylsilyl)amide (KHMDS) to give a sulfur ylide that in the presence of azetidinone **232**, led to the formation of spiroepoxy azetidine **233** *via* a Corey-Chaykovsky epoxidation reaction. This species was shown to undergo a strain-release Meinwald rearrangement[144] in the presence of lithium iodide to give spiro ketone **234**. In this case, the ring expansion of the cyclopropane was observed to give a cyclobutanone product rather than the ring expansion of

the azetidine. Not only is the cyclopropane ring more strained, but it is also better able to stabilise the α-carbocation in intermediate **233'** (see Figure 2).



Scheme 70. Carreira's synthesis and reactivity of a spiroepoxy azetidine.

The epoxidation of alkene **235** with *meta*-chloroperoxybenzoic acid was performed by Williams and co-workers to afford spiroepoxy lactam **236** (Scheme 71a).[145] Again, the reaction with a Lewis acid induced a Meinwald rearrangement, however this time with the ring expansion of the β-lactam to give spirocyclic pyrrolidinone **237**. Worth noting is the reaction of epoxide **238** under the same conditions (Scheme 71b). In this case, after activation of the epoxide with boron trifluoride, ring expansion did not occur, as the 5-membered γ-lactam is far less strained than the β-lactam. Instead, an elimination occurred to give allyl alcohol **239**.



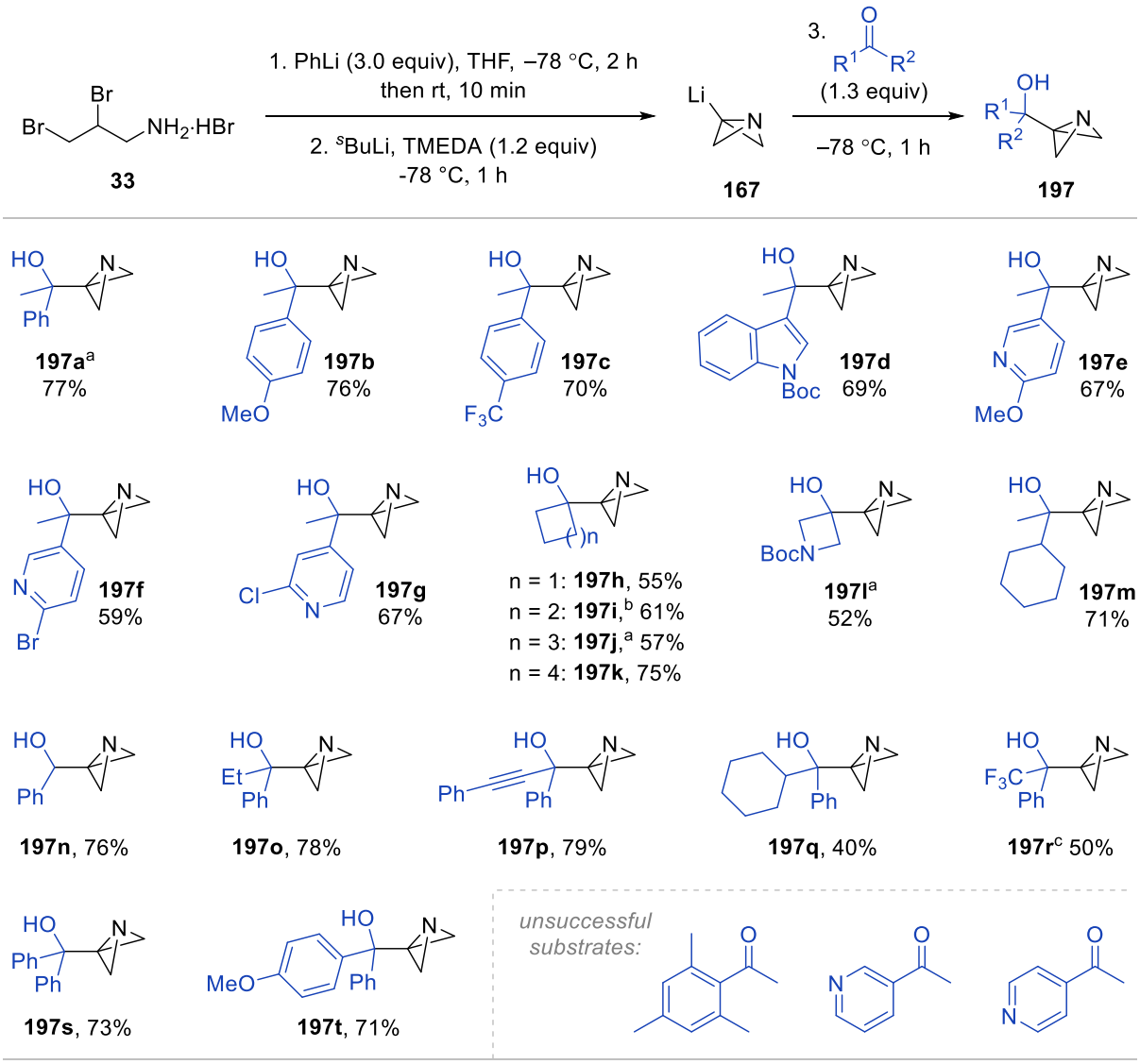
Scheme 71. Williams' synthesis and reactivity of epoxy lactams.

4.4. Results and discussion

4.4.1. Synthesis of azabicyclo[1.1.0]butyl carbinols and initial investigations into strain-release reactivity

To investigate the reaction of ABB-Li with carbonyl compounds, acetophenone was chosen as a model substrate. ABB-Li was formed *in situ* by the sequential reaction of amine salt **33** with phenyllithium and *sec*-butyllithium as described previously (Scheme 72). ABB-Li was

subsequently reacted with acetophenone at −78 °C to form ABB-carbinol **197a** in 77% NMR yield (Scheme 72). An alteration to the procedure for the generation of ABB-Li was made: before the addition of *sec*-butyllithium, the reaction was briefly warmed to room temperature to ensure complete consumption of amine salt **33** that is sparingly soluble in THF. By introducing this warming step, reproducible yields of ABB-carbinol **197a** were obtained.



NMR yields. Reaction conditions: 2.0 mmol scale, 0.31 M initial concentration. [a] 4.0 mmol scale. [b] 1.0 mmol scale. [c] Isolated yield.

Scheme 72. Synthesis of ABB-carbinols by the reaction of ABB-Li with carbonyl compounds.

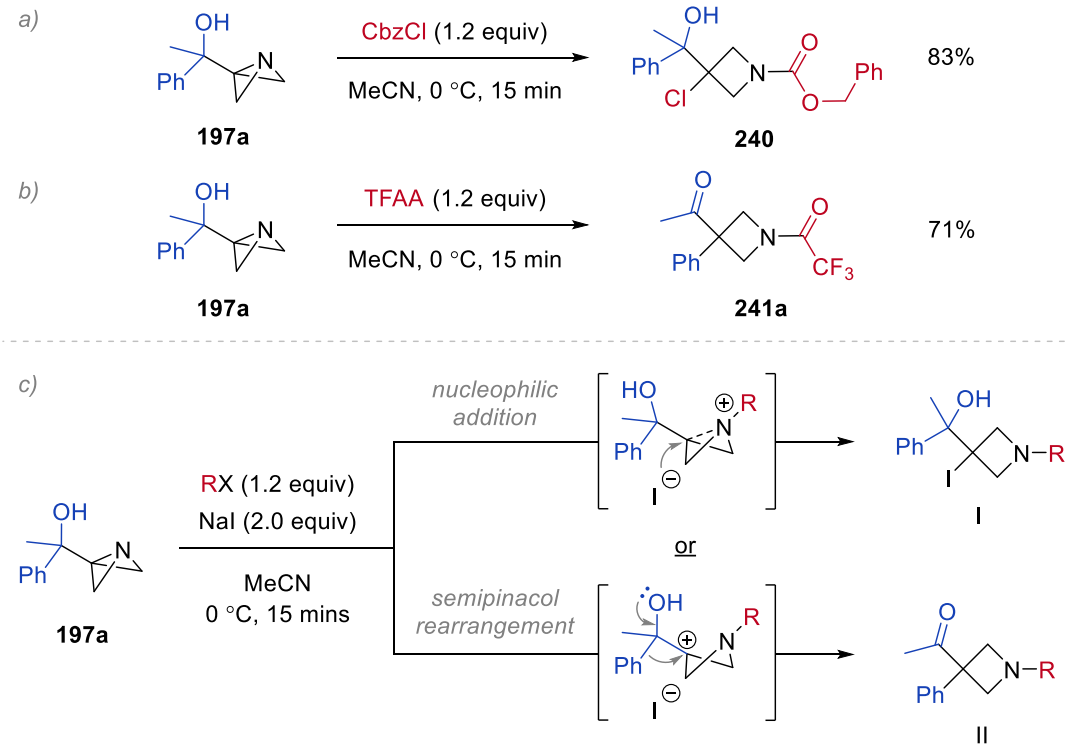
This procedure was successfully applied to a wide range of ketones and aldehydes (Scheme 72). The ABB-carbinols were found to partially decompose on silica gel and so yields of the products were determined by ^{1}H NMR and any subsequent reactions were performed on the crude reaction material. Good yields (60%-79%) were obtained for most substrates, however

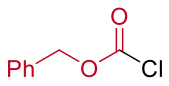
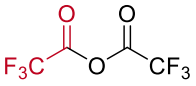
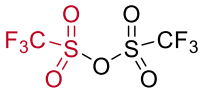
greater steric hindrance around the carbonyl carbon led to a suppression in reaction yield. For example, more hindered cyclohexyl phenyl ketone and 2,2,2-trifluoroacetophenone gave ABB-carbinols **197q** and **197r** in moderate yields of 40% and 50% respectively. 2′,4′,6′-Trimethylacetophenone is even bulkier and, under the reaction conditions, did not yield any desired product. It is reasoned that α-deprotonation by ABB-Li acting as a base instead of a nucleophile is prevalent when the ketone is more sterically hindered. Furthermore, 4-acetylpyridine and 3-acetylpyridine were also unsuccessful substrates. However, by introducing a substituent in the ortho position of the pyridyl ketones, ABB-carbinols **197e**, **197f** and **197g** were obtained in good yields (59%-67%). It was found that ABB-carbinol **197r** was completely stable towards silica gel chromatography, which allowed purification to aid subsequent separations.

Having gained access to a range of ABB-carbinols, their reactivity with different activating agents was then investigated. Firstly, the addition of benzyl chloroformate (CbzCl) to **197a** resulted in the formation of chlorohydrin **240** in 83% yield (Scheme 73a). This result is consistent with previous reports of the 1,3-functionalisation of ABB with chloroformates,[146,52,147] and no spiroepoxy azetidine product was observed. On the other hand, when trifluoroacetic anhydride (TFAA) was employed as the activating agent, a switch in mechanism to the semipinacol rearrangement occurred to form keto azetidine **241a** in 71% yield (Scheme 73b). As expected, the migration of the phenyl group rather than the low migratory aptitude methyl group occurred.

The divergent reactivity of **197a** can be rationalised by the extent of positive charge build-up at the electrophilic bridgehead carbon. When TFAA is used as an activator, the trifluoroacetyl group, being more electron-withdrawing than the Cbz group, results in a greater build-up of positive charge, more resembling a carbocation. It is reasoned that a carbocation α to the alcohol would favour the semipinacol reaction pathway. However, it was postulated that the different counterions present could also play a role in determining the outcome of the reaction. To investigate whether product formation was determined by the nucleophilicity of the counterion or by the electron-withdrawing nature of the activating group, the same reactions were repeated in the presence of sodium iodide additive (Scheme 73c).[148] Once again, with CbzCl, the nucleophilic addition pathway dominated to give exclusively iodohydrin **242**. With TFAA, both nucleophilic addition and semipinacol rearrangement occurred to give **243** and **241a** in 40% and 49% yield, respectively. Finally, when moving to an even more electrophilic activating agent, triflic anhydride (Tf_2O), the semipinacol rearrangement dominated to give

sulfonamide **244a** in 50% yield with no nucleophilic addition observed. Thus, the outcome of the reaction is predominantly determined by the electronic nature of the activating group on nitrogen: the more electron-withdrawing it is the more the semipinacol pathway is favoured.



RX			
I	**242a**, 95%	**243**, 40%	0%
II	0%	**241a**, 49%	**244a**, 50%

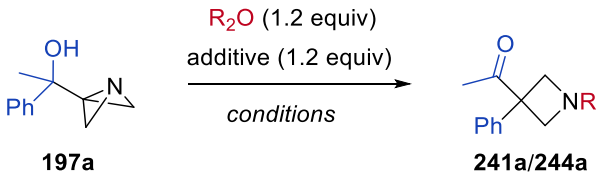
NMR yields. Reaction conditions: 0.1 mmol scale, 0.1 M.

Scheme 73. Divergent reactivity of **197a** with: a) CbzCl and b) TFAA. c) Investigations into the cause of divergence.

4.4.2. Semipinacol rearrangement of azabicyclo[1.1.0]butyl carbinols

4.4.2.1. Optimisation of the semipinacol rearrangement

The semipinacol pathway operating with TFAA and Tf_2O presents a novel route to 1,3,3-substituted azetidines bearing an all-carbon quaternary centre. The choice of TFAA or Tf_2O for the transformation also introduces the opportunity to select one of two nitrogen protecting groups with different properties and lability.[149] Therefore, an optimisation study of this reaction with each activating agent was undertaken (Scheme 74, Table 8).



Scheme 74. Semipinacol rearrangement of ABB-carbinol **197a**.

With TFAA, in the absence of sodium iodide, the yield of **241a** was improved to 93% by changing the solvent to DCM and performing the reaction at –78 °C (Table 8, entry 2). The semipinacol rearrangement reaction of **197a** with TFAA produces 1 equivalent of trifluoracetic acid. It was considered that having a hindered base in solution may improve the reaction yield by quenching the acid formed which might otherwise lead to product decomposition. However, the use of 2,6-lutidine did not improve the yield of **241a** (entry 3).

In the case of Tf_2O, the yield of sulfonamide **244a** was also improved by performing the reaction in DCM at –78 °C (entry 5). Further enhancement in efficiency was observed by the addition of 2,6-lutidine (entry 6), so the more acidic triflic acid produced does in fact have a negative effect on reaction yield.

Table 8. Optimisation of the semipinacol rearrangement of ABB-carbinol **197a**.

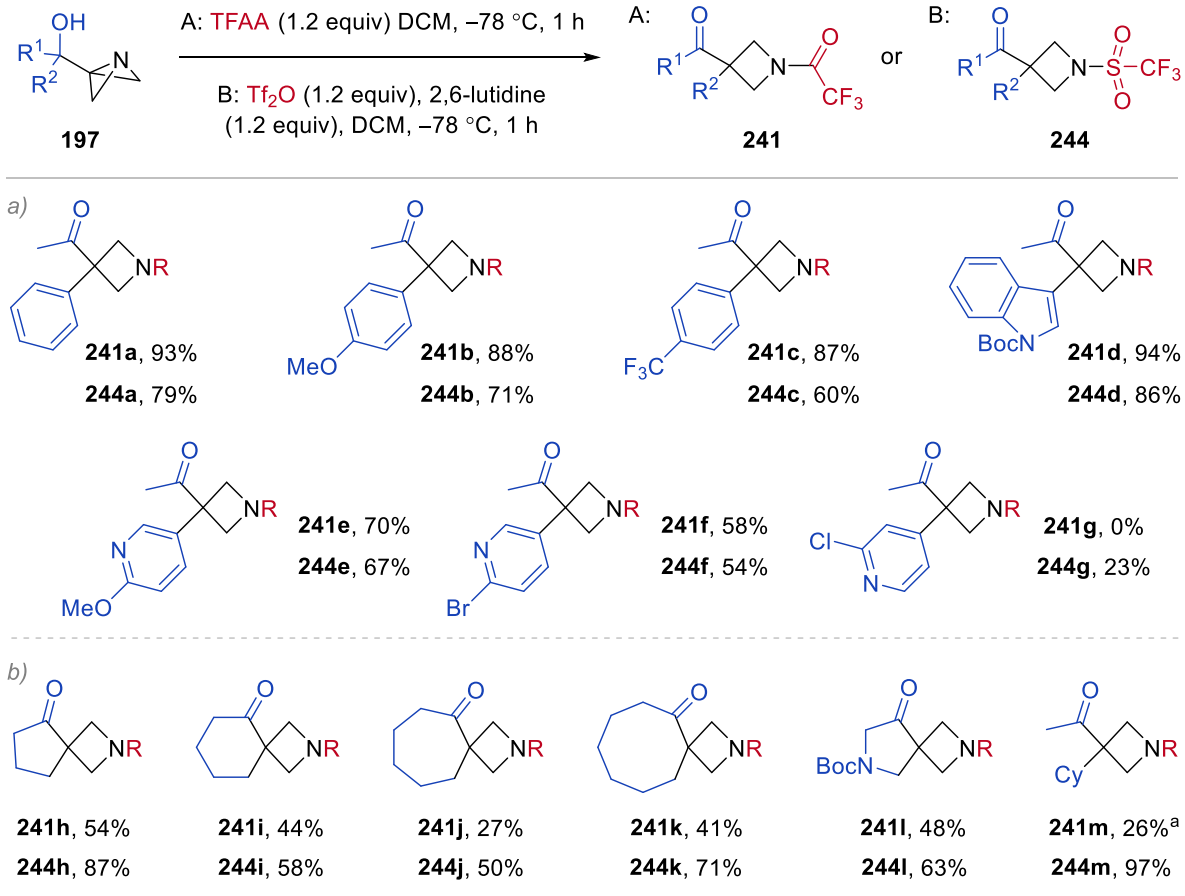
entry	R_2O	additive	solvent	temp, time	yield of **241a**/**244a**
1	$(CF_3CO)_2O$		MeCN	0 °C, 15 mins	71%
2	$(CF_3CO)_2O$		DCM	-78 °C, 1 h	93%[a]
3	$(CF_3CO)_2O$	2,6-lutidine	DCM	-78 °C, 1 h	61%
4	Tf_2O		MeCN	0 °C, 15 mins	40%
5	Tf_2O		DCM	-78 °C, 1 h	67%
6	Tf_2O	2,6-lutidine	DCM	-78 °C, 1 h	79%[a]

NMR yields. Reaction conditions: 0.1 mmol scale, 0.1 M. [a] Performed on a 0.25 mmol scale and isolated yield given.

4.4.2.2. Ketone scope and investigation into relative migratory aptitude

The optimised conditions for the semipinacol rearrangement of ABB-carbinols with either TFAA (conditions A) or Tf_2O (conditions B) were then applied to different ABB-carbinols to evaluate the reaction scope (Scheme 75).

Firstly, with methyl as the non-migrating group, electron rich and electron poor aryl groups migrated smoothly under both conditions to yield azetidines **241b**/**c** and **244b**/**c** in good yields (60%-88%). Furthermore, compounds **241d-f** and **244d-f** were afforded in good to excellent yields *via* the migration of the heteroaryl groups to give indolyl and 3-pyridyl substituted azetidines. While the methoxy and bromo substitution in the ortho position of the pyridyl substrates were required for the synthesis of the precursor ABB-carbinols, these may also deactivate the pyridine nitrogen lone pair towards reacting with the TFAA or Tf_2O rather than the desired ABB nitrogen lone pair. However, the reaction of ABB-carbinol **197g** with a 4-pyridyl substituent was unsuccessful with TFAA and poorly yielding with Tf_2O (23%), which suggests that 4-pyridyl is a poor migrating group.



Isolated yields. Reaction conditions: 0.25 mmol scale,0.1 M. [a] Reaction stirred for 15 min at –78 °C then 30 min at 0 °C.

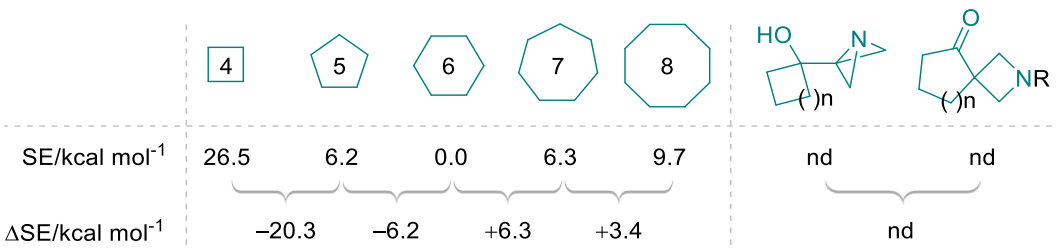
Scheme 75. Reaction scope of the semipinacol rearrangement with aryl and alkyl migrating groups.

The use of ABB-carbinols derived from cyclic ketones was of interest as the semipinacol rearrangement would involve a ring-expansion to give valuable spirocyclic azetidines scaffolds (Scheme 75b). Azetidine **241h** was obtained following a 4- to 5-membered ring expansion from ABB-alcohol **197h** with TFAA in a moderate yield of 54%. ABB-carbinol **197i** was also

employed which led to the formation of azetidine **241i** in 44%. Due to the lower migratory aptitude of alkyl groups compared to aryl groups,[131] some side products were observed in the reaction to produce **241i**. The presence of hydroxyl protons in the crude ^{1}H NMR spectrum and multiple unknown peaks in the ^{19}F NMR spectrum led to the conclusion that competing nucleophilic addition of trifluoroacetate had occured. The yield of this side reaction was difficult to quantify due to the facile decomposition of the product during silica gel chromatography. This side reaction was more prevalent in the preparation of **241j** from ABB-carbinol **197j** following the even less energetically favourable 6- to 7-membered ring expansion. Azetidine **241j** was therefore obtained in a low yield of 27%. Furthermore, a 7- to 8-membered ring expansion was attempted to give azetidine **241k** in 41% yield; again the moderate reaction yield was attributed to competing nucleophilic addition of trifluoroacetate.

Pleasingly, the relative yields of cyclic azetidines **241h-k** (54%, 44%, 27% and 41% respectively), formed under TFAA activation, mirror the differences in strain energy (SE) between the rings in the products and the starting materials (Table 9). It is worth noting however, that the relative SE of unsubstituted cyclic alkanes cannot be assumed to translate to the SE of either the cyclic ABB-carbinols or the spirocyclic ketone products, the SE values of which are unknown.

Table 9. Strain energy difference between simple cyclic alkanes.



The equivalent ring-expansion semipinacol reactions with Tf_2O as the activator gave good yields of sulfonamides **244h-k** (87%, 58%, 50% and 71% yield respectively) with no competing nucleophilic addition observed. Evidently, the more electron-withdrawing activating agent leads to a faster semipinacol rearrangement and so the nucleophilic addition pathway competes less effectively. This effect was demonstrated previously in the experiment outlined in Scheme 73c.

Another successful reaction was the semipinacol rearrangement from ABB-alcohol **197l** to give azetidines **241l** and **244l** in 48% and 63% yield respecitvely.[150] These species comprise an intriguing 2,6-diazaspiro[3.4]octane core with orthogonal nitrogen protecting groups. This

example is particularly noteworthy as a Reaxys search identified this motif in > 250 patents with > 1300 unique examples where pharmacological data is presented.

Moving away from ABB-carbinols derived from cyclic alkyl ketones, ABB-carbinol **197m** was employed, which is derived from acetylcyclohexane. Surprisingly, the migration of the cyclohexyl group was slow with TFAA and required warming to 0 °C to consume starting material **197m**. This resulted in a poor 26% yield of **241m**, and the product of nucleophilic addition of trifluoroacetate was apparent in the crude ^{1}H NMR spectrum. However, with Tf_2O as the activator, the semipinacol rearrangement proceeded smoothly and was favoured completely, giving sulfonamide **244m** in almost quantitative yield. For both reactions, exclusive migration of the more substituted alkyl group was observed.[133]

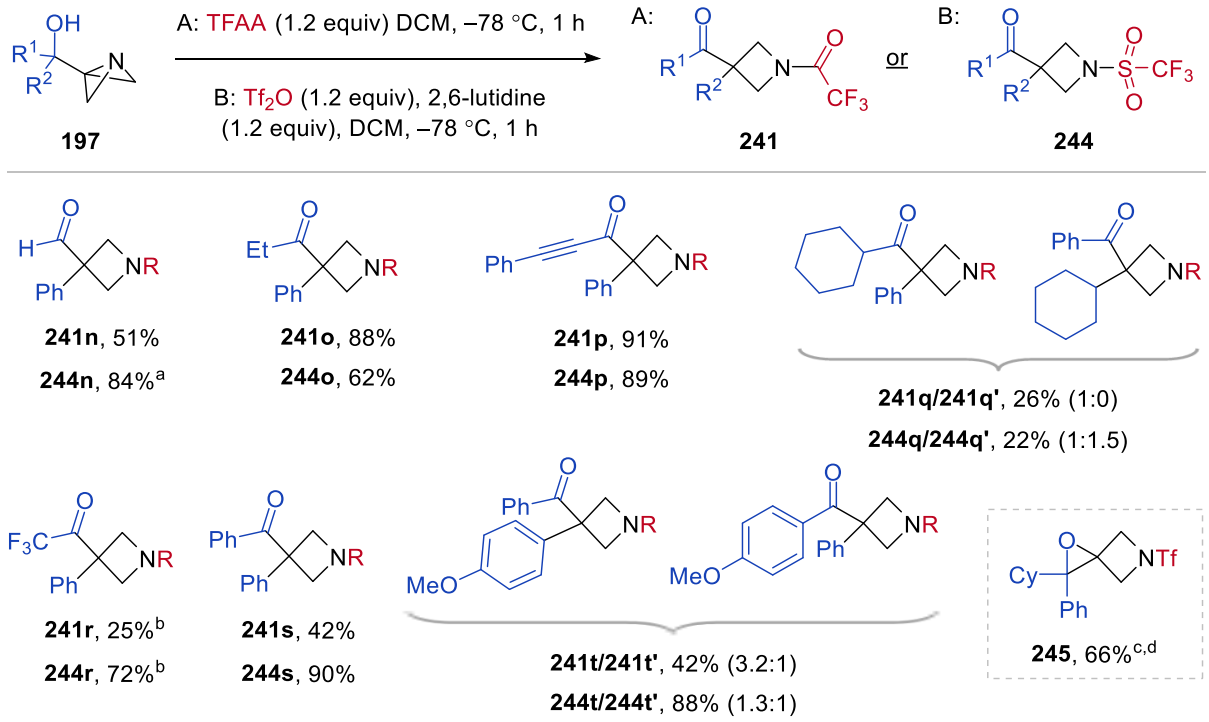
An attribute of the semipinacol rearrangement is that there are two possible migrating groups, and the selectivity of the reaction is governed by the relative migratory aptitudes of these groups. So far, the presence of a poorly migrating methyl group or symmetrical ABB-carbinols has ensured the formation of only one semipinacol reaction product. The evaluation of the relative migratory aptitude of other groups compared to phenyl was then embarked upon (Scheme 76).

With ABB-alcohol **197n**, it was found that the phenyl group migrated exclusively over hydride to give aldehyde **241n** in 51% yield. The selectivity seen here is typical of reported semipinacol rearrangements.[137] Aldehyde **244n** was also prepared however, to aid purification, was reduced with sodium borohydride to give the primary alcohol in 84% yield over two steps. Ethyl and alkynyl groups were also shown to be a successful non-migrating group to give azetidines **241o**/**p** and **244o**/**p** in good to excellent yields (62%-91%).

Comparing the migratory aptitude of phenyl *vs* cyclohexyl by employing ABB-carbinol **197q** resulted in high selectivity for phenyl migration with TFAA to give **241q**. With Tf_2O on the other hand, **244q** and **244q'** were formed in a 1:1.5 ratio, now in favour of cyclohexyl migration. In both cases, the yield of the ketone was low. In fact, the main component of the latter reaction was spirocyclic epoxide **245** formed in 66% NMR yield.

Trifluoromethyl carbinol **197r** was tested and as expected,[151] exclusive migration of the phenyl group was observed. This substrate was substantially less reactive than the others, requiring 0 °C to trigger the semipinacol rearrangement. Azetidine **241r** was formed in only 25% yield with competing nucleophilic addition of trifluoroacetate observed. A much higher yield (72%)

was obtained with Tf_2O (conditions B), giving azetidine **244r**. Both **241r** and **244r** were isolated as a mixture the trifluoromethyl ketone and the corresponding hydrate.[152]



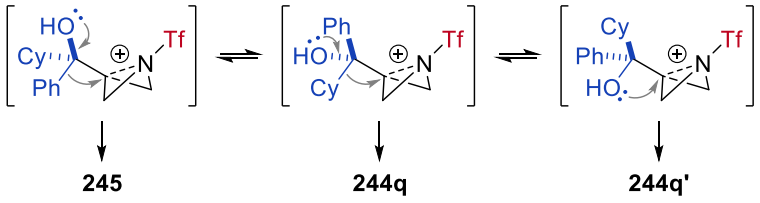
Isolated yields. Reaction conditions: 0.25 mmol scale, 0.1 M. [a] Product isolated after reduction by $NaBH_4$ to the primary alcohol. [b] Reaction stirred for 15 min at –78 °C then 30 min at 0 °C. [c] NMR yield. [d] Formed under conditions B.

Scheme 76. Reaction scope of the semipinacol rearrangement with a phenyl migrating group and alternative non-migrating groups.

Azetidines **241s** and **244s** were obtained from ABB-carbinol **197s** derived from benzophenone in 42% and 90% yields under conditions A and B, respectively. In the case of **241s**, the lower yield observed was due to competing nucleophilic addition of trifluoroacetate. Finally, comparing phenyl with *para*-methoxy phenyl, it was found that the more electron-rich aryl group migrated preferentially,[153] but not exclusively: a 3.2:1 ratio of **241t**/**241t'** and 1.3:1 ratio of **244t**/**244t'** were obtained under conditions A and B, respectively.

The commonly observed relative migratory aptitude in semipinacol rearrangements[131,137,153] of aryl > alkenyl > hydride > substituted alkyl > less substituted alkyl is mirrored here in reactions using TFAA. A similar pattern is seen with the more electron withdrawing Tf_2O activating agent, but the selectivity is lower since it induces a faster and hence less discriminating reaction. This difference in reaction rate and selectivity is illustrated well in the reaction of ABB-carbinol **197t** with only a small electronic difference between the available migrating groups. In the case of the especially hindered substrate **197q**, containing both phenyl and cyclohexyl migrating groups, no selectivity is observed with Tf_2O. Perhaps in this case, C–C

bond rotation at the bridgehead of ABB-carbinol **197q** has a higher energy barrier than 1,2-migration or intramolecular epoxide formation. This would mean that whichever group is antiperiplanar to the central C–N upon reaction with Tf_2O is the group to react (Scheme 77).

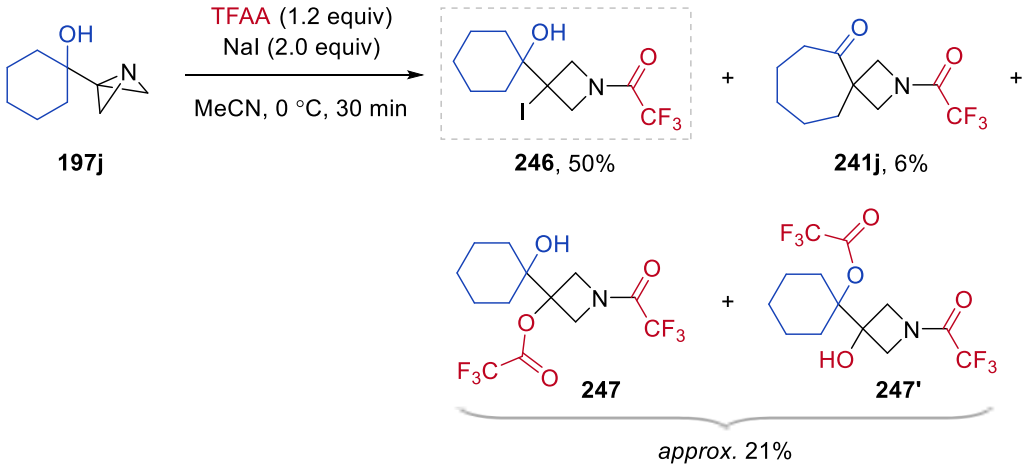


Scheme 77. Conformations of ABB-carbinol **197q** activated my Tf_2O that lead to each of the three products observed.

4.4.2.3. Attempts to improve yields for poorly migrating substrates

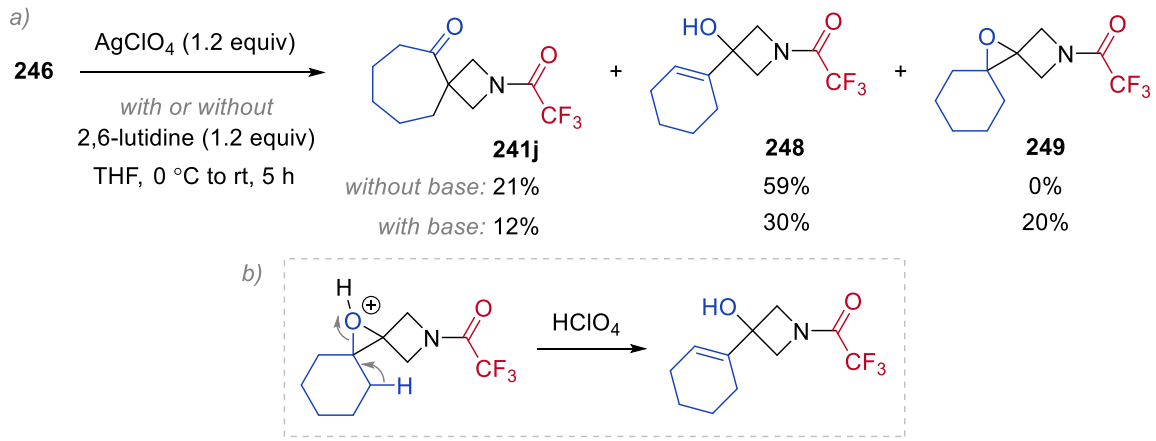
In response to lower yields observed in the TFAA induced semipinacol rearrangement reaction of ABB-carbinols with poor migrating groups, alternative reaction conditions were investigated. It was considered that iodohydrin **243**, formed from the reaction of ABB-carbinol **197a** with TFAA and sodium iodide (see Scheme 73c), could serve itself as a precursor to a semipinacol rearrangement reaction. It was anticipated that the addition of a silver(I) salt to **243** would result in the formation of a full carbocation at the 3-position of the azetidine which would trigger a fast semipinacol rearrangement.[127]

To investigate this reaction, ABB carbinol **197j** was chosen as a substrate as it performed poorly in the semipinacol reaction induced by TFAA (27% yield). On the addition of TFAA to **197j** in the presence of sodium iodide, iodohydrin **246** was formed in 50% yield and the semipinacol rearrangement proceeded in only 6% yield (Scheme 78). The remaining mass balance was made up of a mixture of two inseparable species the characterisation of which proved difficult. The ^{19}F NMR spectrum contained four signals, two characteristic of a trifluoroacetamide and two characteristic of a trifluoroacetate. Additionally, the presence of hydroxyl signals in the ^{1}H NMR led to assignment that the side products are likely isomers **247** and **247'** which arise from the nucleophilic addition of trifluoroacetate to the ABB-carbinol.



Scheme 78. Synthesis of iodohydrin **246** other reaction products.

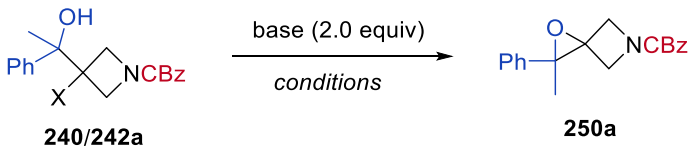
It was found that upon the addition of silver perchlorate to iodohydrin **246**, a mixture of products was obtained (Scheme 79a). Once again, the semipinacol rearrangement to keto azetidine **241j** was not very efficient (21%) and the major product obtained was allyl alcohol **248** in 59% yield. It was demonstrated previously by Williams[145] that spiroepoxy γ-lactam **238** underwent an acid catalysed rearrangement to allyl alcohol **239** (see Scheme 71b), which resembles the product formed here. To establish whether **248** was in fact produced from spiroepoxy azetidine **249** (Scheme 79b), the reaction was repeated with the addition of 2,6-lutidine as a base to quench any perchloric acid produced. Indeed, alcohol **248** was still formed under these conditions, but epoxide **249** was also isolated as a reaction product (Scheme 79a). Nevertheless, it was clear that the semipinacol rearrangement of iodohydrins by the addition of silver perchlorate did not present as an improvement over the direct TFAA induced semipinacol rearrangement from the parent ABB-carbinol.



Scheme 79. Reaction of iodohydrin **246** with silver perchlorate.

4.4.3. Spiroepoxy azetidine formation reaction

The formation of spiroepoxy azetidines **245** and **249** were intriguing, and it was considered whether a general pathway to these interesting motifs could be established. It was reasoned that chlorohydrin **240**, formed from the reaction of ABB-carbinol **197a** with CbzCl (Scheme 73a), could potentially serve as an intermediate in the selective synthesis of spiroepoxy azetidines by the addition of base (Scheme 80).



Scheme 80. Epoxide ring-closing of halohydrin azetidines **240** and **242a**.

Indeed, addition of potassium carbonate to a solution of **240** in methanol resulted in the formation of spiroepoxy azetidine **250a**, which after 2.5 hours had reached 57% yield with 7% remaining unreacted starting material (Table 10, entry 1). Moving to stronger bases, sodium hydride and sodium *tert*-butoxide improved the yield considerably and the reactions were also complete in a shorter amount of time (entries 2 and 3). However, we were eager to avoid the use of a strong base as applying this methodology to other more sensitive ABB-carbinols could be deleterious to reaction yields. The use of iodohydrin **242a** instead of chlorohydrin **240**, was then considered as the epoxide ring-closure should be more facile with the more labile iodide leaving group. Pleasingly, the addition of potassium carbonate to a solution of **242a** in methanol gave the desired product quantitatively within 15 minutes at room temperature.

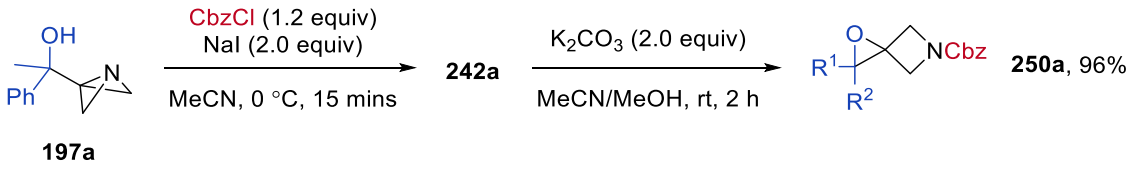
Table 10. Reaction condition screening for the epoxide ring-closing of halohydrin azetidines **240** and **242a**.

entry	X (**240**/**242a**)	base	solvent	temp, time	yield of **250a**
1	Cl	K_2CO_3	MeOH	rt, 2.5 h	57%
2	Cl	NaH	THF	rt, 30 min	89%
3	Cl	NaO^tBu	THF	rt, 1.5 h	80%
4	I	K_2CO_3	MeOH	rt, 15 min	100%[a]

NMR yields. Reaction conditions: 0.05 mmol scale, 0.1 M. [a] Performed on a 0.25 mmol scale and isolated yield given.

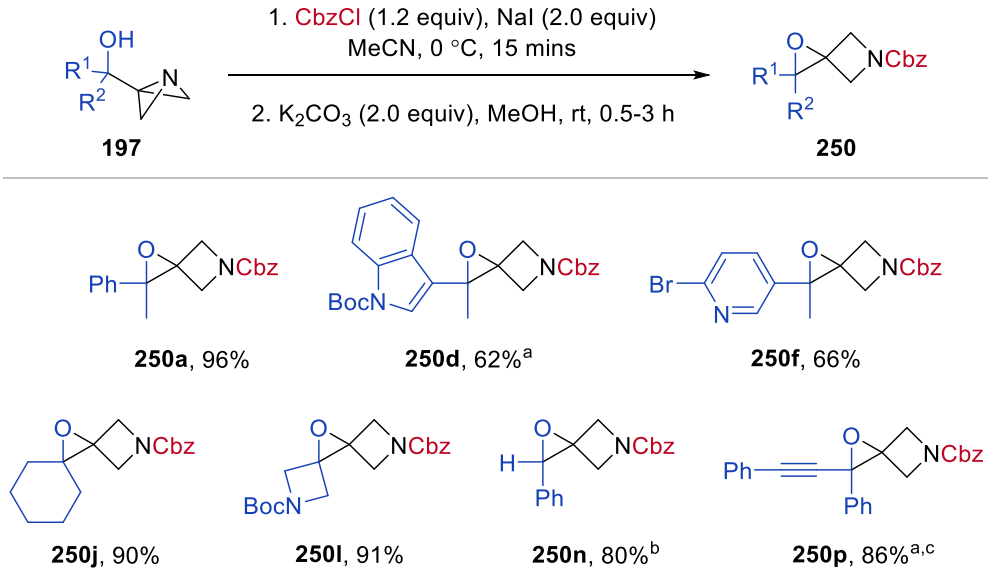
This method was telescoped to a one-pot procedure from ABB-carbinol **197a**, in which a longer time for the spirocyclisation step was required due to the lower solubility of potassium

carbonate in the acetonitrile/methanol solvent mix. Nevertheless, it was possible to monitor the reaction by TLC and after 2 hours, **250a** was formed in 96% yield over two steps (Scheme 81).



Scheme 81. One-pot spiroepoxy azetidine synthesis from ABB-carbinol **197a**.

This protocol was then extended to produce a range of spiroepoxy azetidines from selected ABB-carbinols (Scheme 82). Employing ABB-carbinols with heteroaryl groups (indolyl and pyridyl) gave **250d** and **250f** in good yields of 62% and 66%, respectively. Electron-rich indolyl epoxide **250d** was found to be unstable on silica gel, which complicated the purification. However, it was found that if the intermediate iodohydrin was purified prior to base-induced spirocyclization, no further purification of **250d** was necessary.



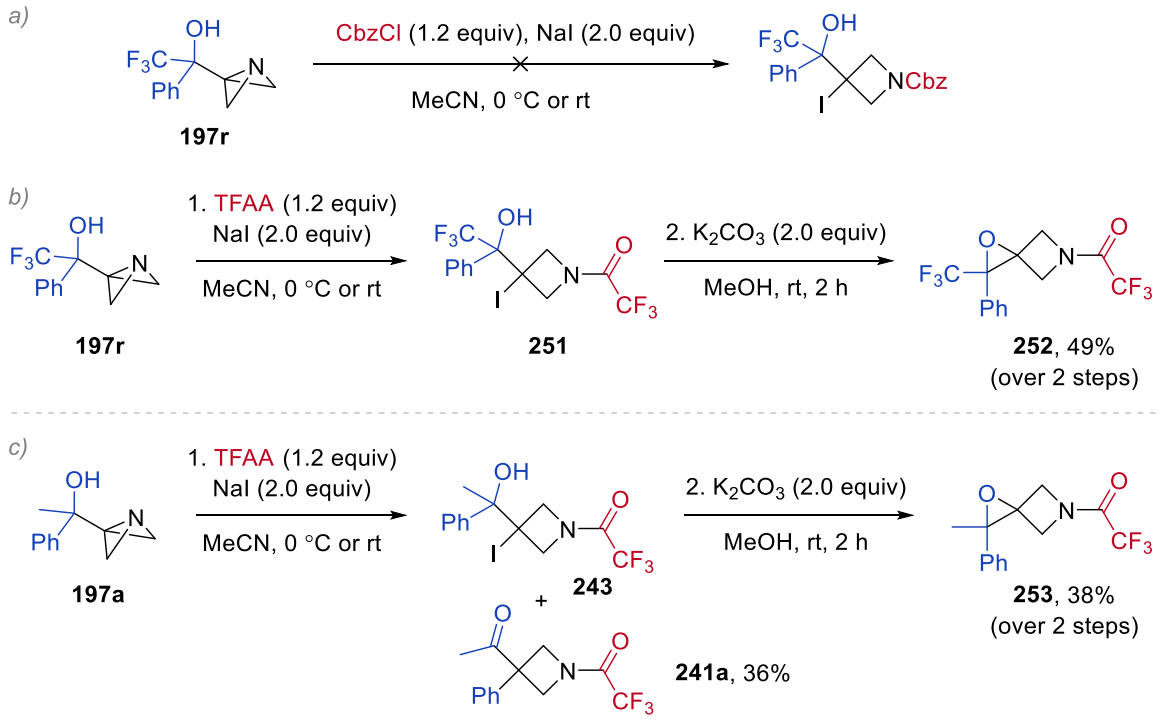
Isolated yields. Reaction conditions: 0.25 mmol scale, 0.1 M initial concentration. [a] Intermediate iodohydrin isolated before second step. [b] Reaction stirred for 42 h after addition of K_2CO_3. [c] 0.05 M initial concentration.

Scheme 82. Scope of the spiroepoxy azetidine formation reaction.

Dispiro compounds **250j** and **250l** were obtained from ABB-carbinols **197j** and **197l** in excellent yields of 90% and 91%, respectively. Compound **250l** is particularly interesting, as the nitrogen protecting groups are orthogonal and serve to desymmetrise the molecule. Trisubstituted epoxide **250n** was also accessible in 80% yield from benzaldehyde derived ABB-carbinol **197n**. With less substitution, the rate of cyclization was much slower and

required 42 hours to reach completion. The sensitive propargylic epoxide **250p** was also accessible in excellent yield (86%). Due to its instability on silica gel (as with **250d**), purification of the intermediate iodohydrin was necessary in order to isolate analytically pure **250p**.

Remarkably, ABB-alcohol **197r** was found to be completely unreactive towards CbzCl under the reaction conditions, due to inductive deactivation of the nitrogen lone pair by the CF_3 group (Scheme 83a). In addition, the semipinacol rearrangement of **197r** with TFAA was previously found to be slow and low yielding. It was found that in the presence of sodium iodide, the formation of iodohydrin product **251** is preferential over the semipinacol rearrangement and after the addition of potassium carbonate, epoxide **252** was isolated in 49% yield (Scheme 83b).

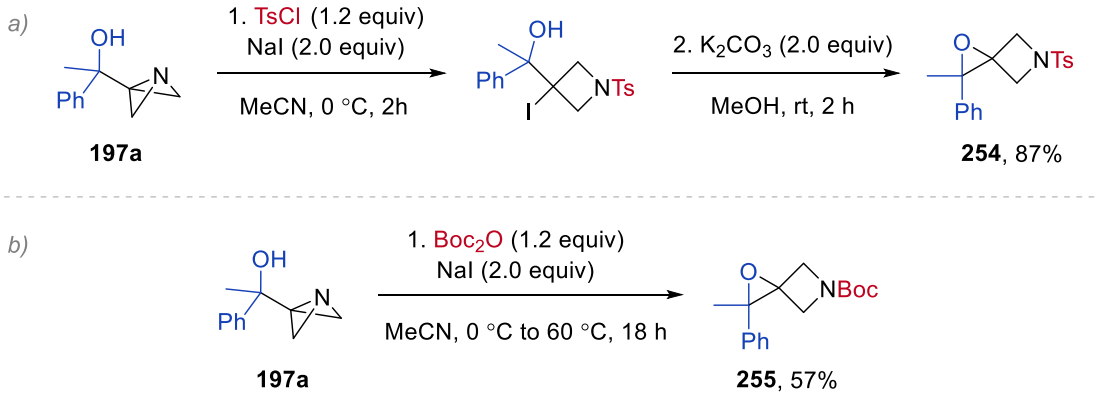


Scheme 83. Further investigation into the scope of the spiroepoxy azetidine formation reaction with TFAA as the activator.

Having established that the addition of TFAA to **197a** in the presence of sodium iodide resulted in the formation of iodohydrin **243** and semipinacol rearrangement product **241a** (see Scheme 73c), the addition of potassium carbonate to this mixture led to the formation of epoxide **253** in 38% yield (Scheme 83c).

When investigating alternative activating agents, it was found that TsCl behaved similarly to CbzCl to give sulfonamide **254** in 87% yield (Scheme 84a). Di-tert-butyl dicarbonate (Boc_2O), on the other hand, was much slower to react and required heating to reflux overnight to activate

ABB-alcohol **197a**. However, under these conditions, cyclisation followed iodohydrin formation to give epoxide **255** in 57% yield without the need for the addition of potassium carbonate.



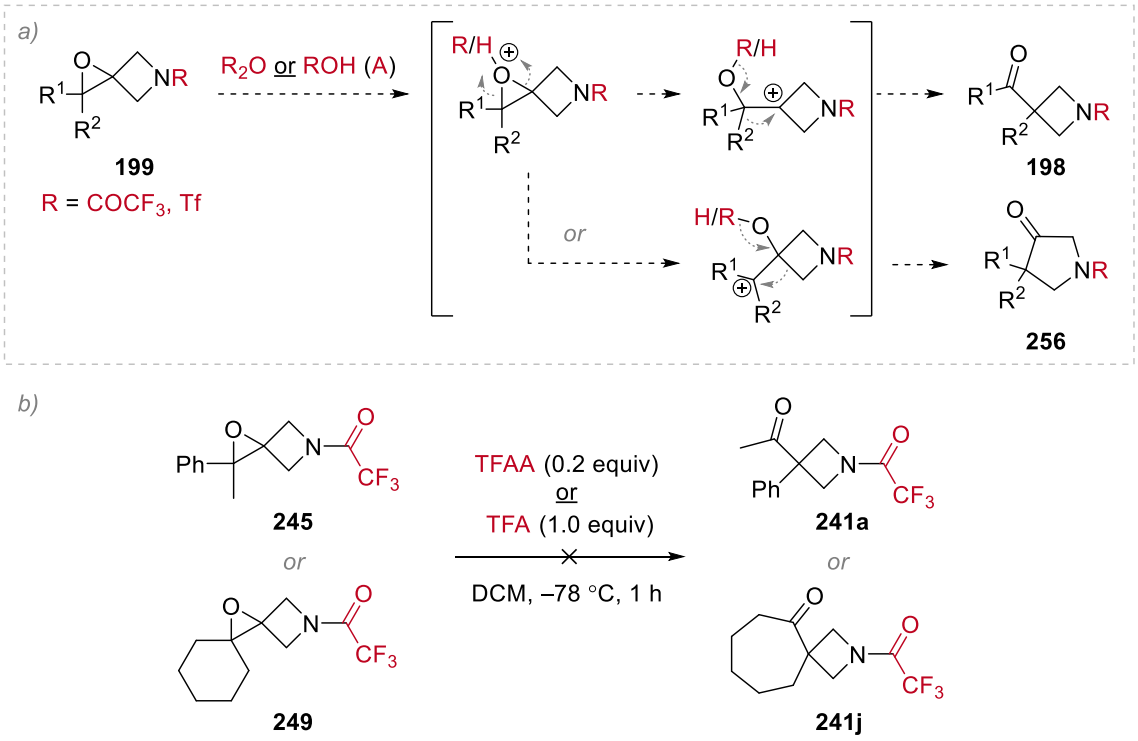
Scheme 84. Spiroepoxy azetidine formation reaction with alternative activating agents.

4.4.4. Investigation into the semipinacol reaction mechanism

Having established the divergent reactivity of ABB-carbinols, a further examination of reaction mechanism was undertaken. We previously observed that the reaction of ABB-carbinol **197a** with more electron-withdrawing activating agents (TFAA or Tf_2O) favoured the semipinacol reaction pathway (see Scheme 73c). However, it is known that under certain conditions, epoxides can undergo a pinacol-type Meinwald rearrangement to give ketone products (see Scheme 68b for an example).

We cannot yet rule out the possibility that activation of an ABB-carbinol with 1.2 equivalents of TFAA or Tf_2O leads to the formation of an epoxide that then undergoes a Meinwald rearrangement under the reaction conditions (Scheme 85a). This mechanism is unlikely to be occurring for a number of reasons. Principally, after activation of the epoxide with either the excess anhydride or acid biproduct, there are two possible carbocations that can be formed. In most substrates investigated, one of the substituents R^1 or R^2 is an aryl group that would effectively stabilise a benzylic carbocation. This would not give azetidine **198** as the reaction product, rather ring expanded pyrrolidine **256**.

To rule out the possibility of a Meinwald rearrangement mechanism rather than a direct semipinacol rearrangement, the reaction conditions were simulated by reacting epoxides **245** and **249** with either 0.2 equivalents of TFAA or 1.0 equivalent of TFA in DCM at −78 °C. In all four reactions, no Meinwald rearrangement occurred and epoxides **245** and **249** were recovered quantitatively.



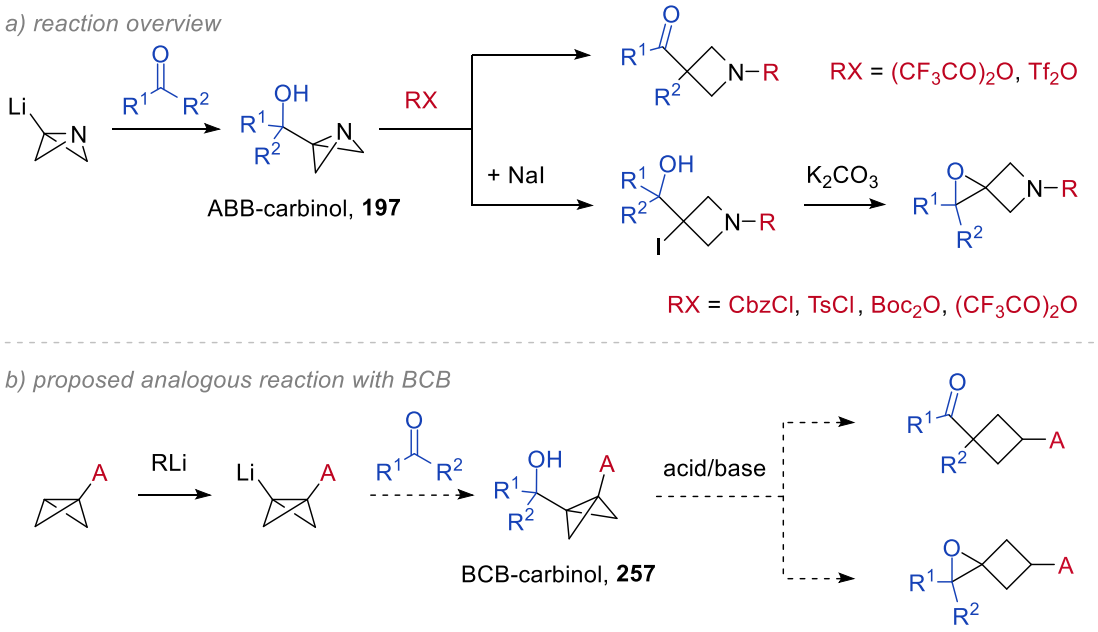
Scheme 85. Investigation into whether the spiroepoxy azetidine is a reaction intermediate in the semipinacol rearrangement.

4.4.5. Conclusion

The lithiation of ABB followed by 1,2-addition to ketones and aldehydes has been achieved to yield ABB-carbinols. These species were demonstrated to undergo divergent strain-release reactivity when reacted with electrophilic activating agents.

We found that strongly electrophilic activating reagents (TFAA and Tf_2O) induce a semipinacol rearrangement in ABB-carbinols to give either amide or sulfonamide azetidine products (Scheme 86a). The semipinacol rearrangement proceeds with migration of the group best able to stabilize the positive charge, so follows the order aryl > substituted alkyl > less substituted alkyl. Even electron-deficient aromatics and heteroaromatics were demonstrated to migrate in preference to alkyl groups.

When two alkyl groups are present, the semipinacol rearrangement is much slower and in the case of TFAA as the activator, nucleophilic addition of the counterion begins to compete, leading to lower yields. However, employing Tf_2O as the activator allows the semipinacol rearrangement to dominate, leading to good reaction yields. It was demonstrated that ABB-carbinols derived from cyclic ketones give valuable spirocyclic azetidine products after 1,2-alkyl migration.

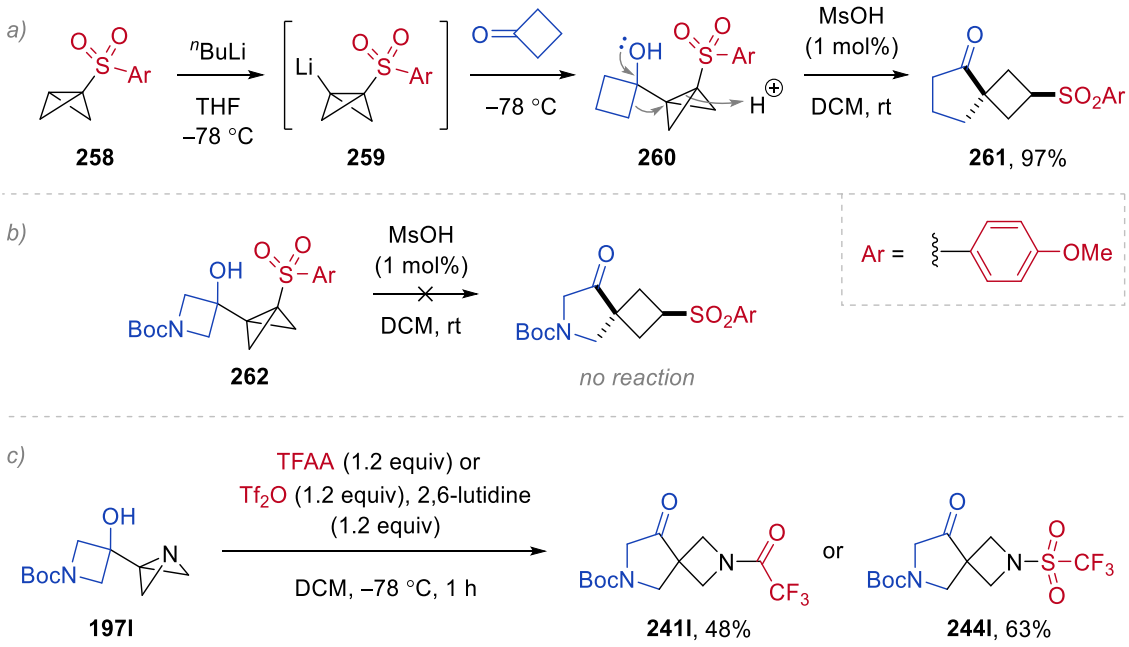


Scheme 86. Overview of the divergent reactions of ABB-carbinols.

Conversely, when ABB-carbinols are treated with less electrophilic activating agents, such as CbzCl, no semipinacol rearrangement occurs. Instead, nucleophilic addition of the counterion dominates to exclusively form chlorohydrin products. Performing this reaction in the presence of sodium iodide leads to the formation of iodohydrins that can be easily converted into structurally interesting spiroepoxy azetidines through a base-mediated cyclization (Scheme 86a). Thus, from a common ABB-carbinol starting material, access to either keto azetidines or spiroepoxy azetidines is possible through semipinacol rearrangements and spirocyclisation reactions, respectively.

As the chemistry of ABB generally resembles that of BCBs that bear an electron withdrawing group (see sections 1.2.2 and 1.2.3), it was considered whether these novel reactivity modes could be extended to bicyclo[1.1.0]butyl carbinols (BCB-carbinols, **257**, Scheme 86b). However, very recently, the synthesis and reactivity of some BCB-carbinols has in fact been reported by Wipf and co-workers (Scheme 87a).[154] This investigation took place simultaneously and independently of our own studies and provides an interesting comparison.

Wipf and co-workers deprotonated BCB-sulfone **258** with *n*-butyllithium to afford organolithium **259** that was reacted with cyclobutanone to give BCB-carbinol **260**. With the addition of catalytic methanesulfonic acid (MsOH), a stereoselective semipinacol rearrangement of **260** occurs to give spirocycle **261**.



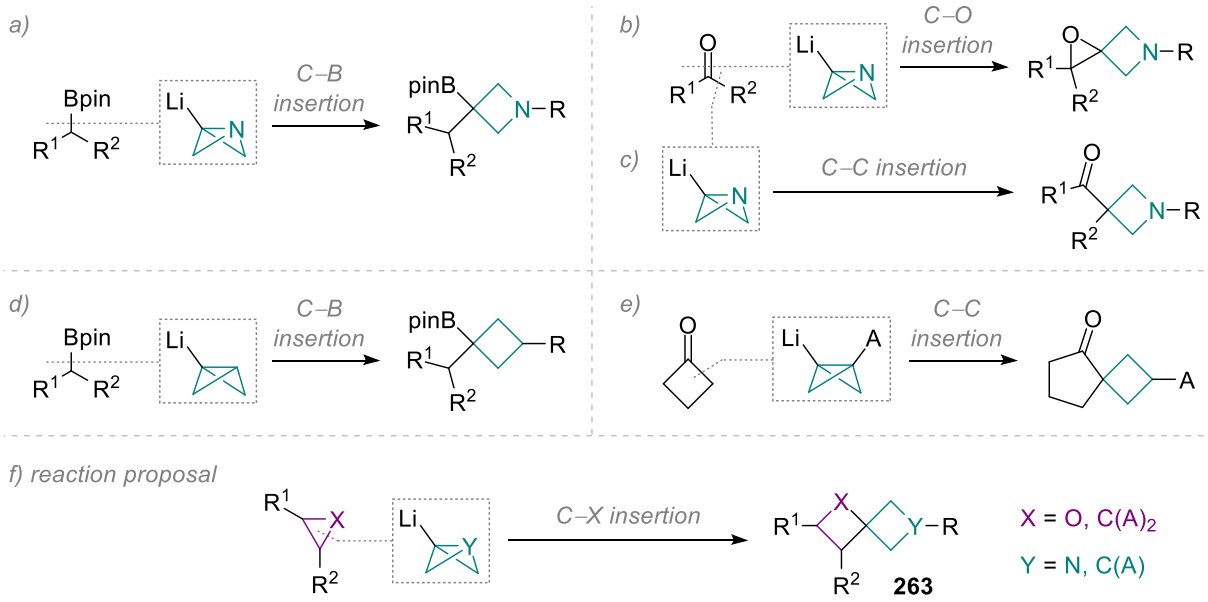
Scheme 87. a)/b) Wipf and coworkers' semipinacol rearrangement of BCB-carbinols. c) Comparison to the semipinacol rearrangement of ABB-carbinols reported herein.

The reaction scope presented is limited to BCB-carbinols derived from cyclobutanones with one example of a BCB-carbinol derived from 3-oxetanone. Therefore, all semipinacol rearrangements were 4- to 5-membered ring expansions which have an additional strain-release driving force than just that of the BCB motif. Furthermore, BCB-carbinol **262**, derived from 1-Boc-3-azetidinone, was shown to be inert under the reaction conditions (Scheme 87b), which is in direct contrast to our successful synthesis of azetidines **241l** and **244l** (Scheme 87c). These results give insight into the differences in reactivity between BCB and ABB. While their thermodynamic strain energy is assumed to be very similar,[41,155] ABB is far more kinetically activated due to the availability of the nitrogen lone-pair to react with electrophiles.

4.4.6. Future work

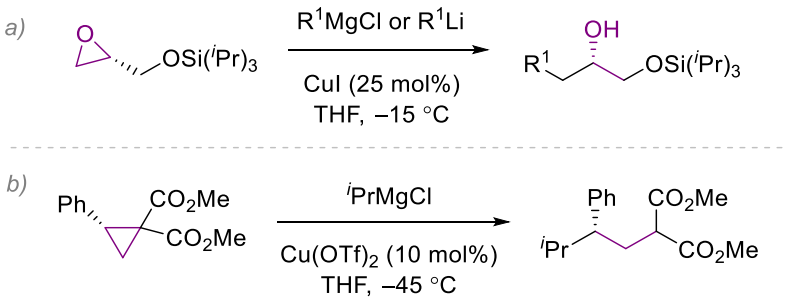
The reactions of ABB-Li presented in this chapter, and previously in chapter 3, can be described as insertion reactions (Scheme 88a-c). Specifically, the reaction of ABB-Li with boronic esters followed by 1,2-metallate rearrangement overall represents the homologation of a boronic ester with an azetidine. This is essentially the insertion of an azetidine into the C–B bond (Scheme 88a). The reactions of this chapter represent the insertion of an azetidine ring into the C–O or C–C bond of a ketone or aldehyde (Scheme 88b/c). This analysis can be extended to reported reactions of BCB-Li derivatives (Scheme 88d/e).[80,81,154] Using this thinking, access to spiro[3.3]heptane derivatives, such as **263**, would require the insertion of ABB or BCB into a 3-membered ring, for example an epoxide or a DA cyclopropane (Scheme

88f). Such spirocycles are sought-after motifs in medicinal chemistry,[140,141] particularly if they contain an oxetane[156] or azetidine ring.[157]



Scheme 88. Reactions of lithiated bicycles and proposed spirocyclisation reaction.

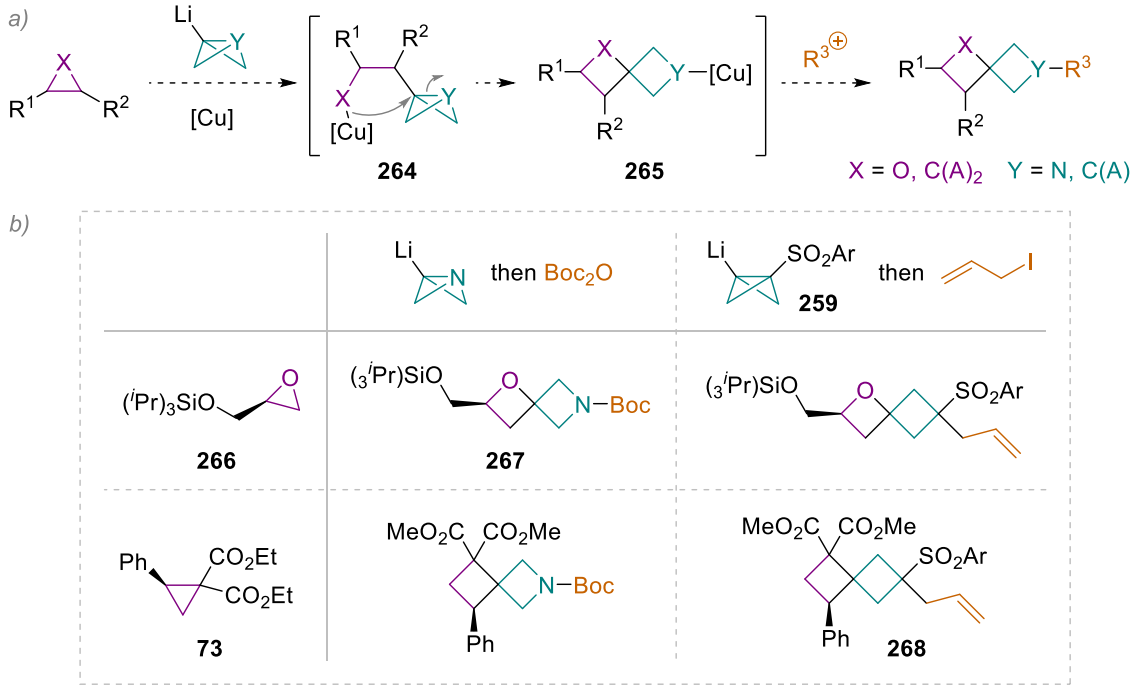
The nucleophilic ring opening of epoxides and DA cyclopropanes with organometallic reagents is known reactivity (Scheme 89). This typically involves the use of a Grignard or organolithium reagent and a copper catalyst.[158,159] Similarly, the copper-catalysed nucleophilic addition of Grignard reagents to both ABB and an electron deficient BCB have been reported (see Scheme 6 and Scheme 9).[39,54]



Scheme 89. Nucleophilic ring opening of 3-membered rings by organometallic reagents.

It would be interesting to investigate whether ABB-Li or an electron deficient BCB-Li could undergo nucleophilic addition to epoxides or DA cyclopropanes in the presence of a copper catalyst (Scheme 90a). Such a reaction would give strained cuprate **264** that could undergo a strain-release intramolecular cyclisation to give spirocyclic compound **265**. The addition of an electrophile to quench **265** would introduce another opportunity for diversification. If successful, this 3-component approach would be an efficient method to access a wide variety

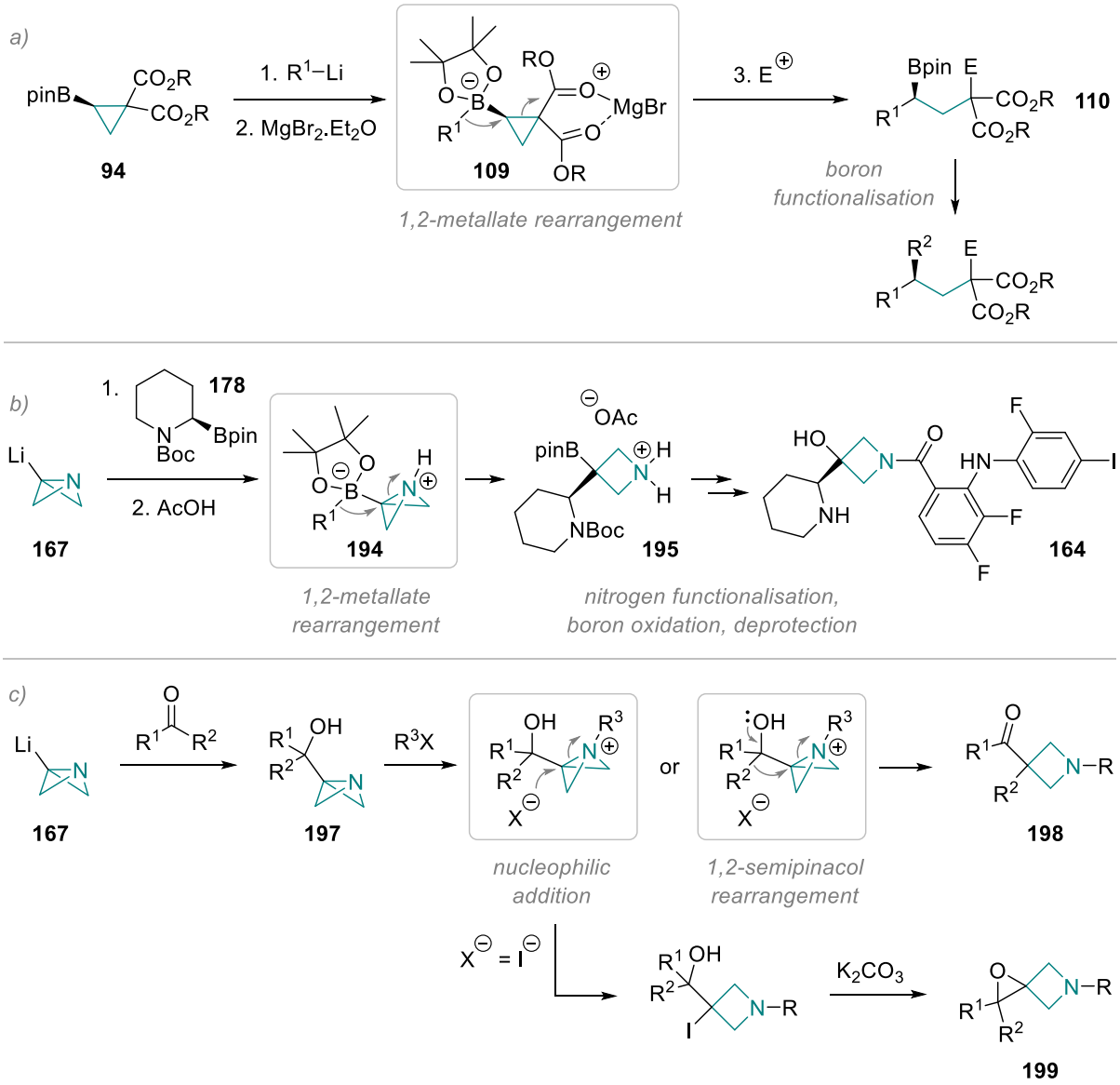
of spiro[3.3]heptane derivatives with various heteroatoms and substitution patterns (Scheme 90b). For example, pairing epoxide **266** with ABB-Li could lead to the formation of 1-oxa-6-azaspiro[3.3]heptane **267**. Alternatively, the combination of DA cyclopropane **73** and BCB-Li **259** could give all-carbon spiro[3.3]heptane **268**.



Scheme 90. Proposed synthesis of spiro[3.3]heptane derivatives.

5. General conclusion

Investigations into new strain-release-driven transformations were undertaken. This was conducted with the aim of establishing efficient, modular routes to diversely decorated molecules with interesting molecular scaffolds. The strain-release of the activated C–C bond of DA cyclopropanes and the bridge bond of ABB has facilitated the synthesis of a diverse set of highly functionalised 3-dimensional molecules (Scheme 91). The main class of reaction mechanism explored was strain-release 1,2-migration, namely, the 1,2-metallate rearrangement of boronate complexes and the 1,2-semipinacol rearrangement reaction.



Scheme 91. Overview of the reactions investigated in this thesis.

It was demonstrated that cyclopropyl boronate complexes **109** with two ester substituents undergo an enantiospecific 1,2-metallate rearrangement upon the addition of a Lewis acid

(Scheme 91a). The 1,2-migration is driven by the cleavage of the strained, activated cyclopropyl C–C bond. A scope of migrating groups was presented by the addition of a variety of different organolithium reagents to cyclopropyl boronic ester **94**. This process was also rendered a 3-component reaction by the use of sub-stoichiometric Lewis acid and the addition of an electrophile. This enabled the synthesis of enantioenriched γ-carbonyl boronic esters **110**. In addition, the products were shown to be suitable substrates for further enantiospecific transformations of the boronic ester functional group.

A reactivity study was also undertaken, which indicated that the 1,2-metallate rearrangement with C–C cleavage only occurs if the C–C bond is incorporated into a strained cyclopropane ring. In addition, the presence of two ester substituents was shown to be necessary for the desired reaction to occur.

The use of the strained bridge bond of ABB was then investigated as a driving force for the 1,2-metallate rearrangement (Scheme 91b). The addition of ABB-Li (**167**) to boronic ester **178** led to the formation of boronate complex **194** that, upon activation with acetic acid, underwent the 1,2-metallate rearrangement with cleavage of the strained C–N bridge bond. The product of this reaction is azetidine acetic acid salt **195**. This species was subjected to amide bond coupling conditions, followed by boronic ester oxidation, and finally Boc deprotection to yield anti-cancer drug cobimetinib (**164**). This short reaction sequence demonstrates the utility of ABB-Li in the synthesis of valuable complex molecules.

ABB-Li was then employed in the synthesis of other interesting azetidine-containing molecules (Scheme 91c). It was found that ABB-Li reacts smoothly with ketones and aldehydes to yield ABB-carbinols **197**. These species display divergent strain-release reactivity upon activation of the ABB nitrogen lone pair with different activating agents. With strongly electrophilic activating agents TFAA and Tf_2O, a semipinacol rearrangement occurs with 1,2-migration of one of the alcohol substitutents. This leads to the formation of azetidinyl ketones **198** with an all-carbon quaternary centre. The relative migratory aptitude of different groups was explored by employing a range of ABB-carbinols with varying substituents.

However, it was shown that the semipinacol rearrangement does not occur when ABB-carbinols are reacted with less electrophilic activating agents such as CbzCl. In this case, after activation of the ABB nitrogen, nucleophilic addition of the counterion to the C3 carbon occurs. When this reaction is performed in the presence of sodium iodide, this mechanism results in

the formation of iodohydrins, which can be converted into spiroepoxy azetidines **199** simply by the addition of potassium carbonate.

Overall, novel strain-release reactions of DA cyclopropanes and ABB derivatives were demonstrated, which enabled the synthesis of a diverse set of structurally interesting, highly functionalised molecules.

6. Experimental

6.1. General experimental

6.1.1. Solvents, reagents and glassware

All solvents were commercially supplied or dried on an Anhydrous Engineering alumina column drying system. All reactions were conducted under an inert atmosphere of nitrogen using standard Schlenk techniques unless stated otherwise. All glassware was oven dried prior to use. All reagents were purchased from commercial sources and used as sold. Exceptions: di-*tert*-butyl malonate and 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (^{i}PrOB(pin)) were distilled under reduced pressure using Kugelrohr apparatus; pinacolborane (HBpin), benzoyl chloride, benzyl chloroformate, TMEDA, *N*,*N*-diisopropylethylamine and triethylamine were distilled under an inert atmosphere at standard pressure; all liquid ketone/aldehyde reagents and styrene containing starting materials were filtered through neutral alumina prior to use.

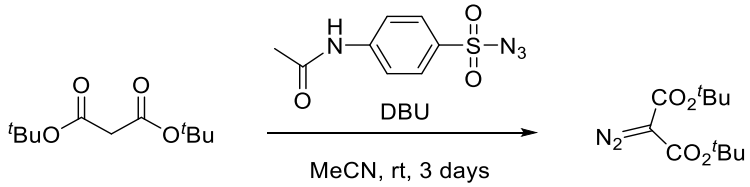
6.1.2. Chromatography and spectroscopy

All reactions were followed by thin-layer chromatography (TLC) when practical, which were visualised under UV light or by staining with aqueous potassium permanganate, phosphomolybdic acid or *p*-anisaldehyde solutions. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded using Jeol ECS 400 MHz, Jeol ECz 400 MHz, Bruker 400 MHz and Bruker Avance III HD 500 MHz Cryo spectrometers. ^{11}B NMR spectra were recorded using a Jeol ECP(Eclipse) 300 MHz and Jeol ECS 400 MHz spectrometers using a quartz NMR tube. Chemical shifts (δ) are given in parts per million (ppm) and coupling constants (J) are given in Hertz (Hz), rounded to the nearest 0.1 Hz. NMR assignments were made according to spin systems, using two-dimensional NMR spectroscopy (COSY, HSQC, HMBC) to assist the assignment. NMR yields were determined using tetrachloroethylene or dibromomethane as an internal standard. High resolution mass spectra (HRMS) were recorded by Bruker Daltonics Apex IV by Electrospray Ionisation (ESI) or Atmospheric pressure chemical ionization (APCI). IR spectra were recorded on a Perkin Elmer Spectrum One FT-IR as a thin film. Absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}). Melting points were recorded in degrees Celsius (°C) using a Stuart SMP30 melting point apparatus. Optical rotations were measured in $CHCl_3$ using a Bellingham & Stanley ADP 220 Polarimeter.

6.2. Synthetic procedures for chapter 2

6.2.1. Starting material synthesis

Di-*tert*-butyl 2-diazomalonate, 102

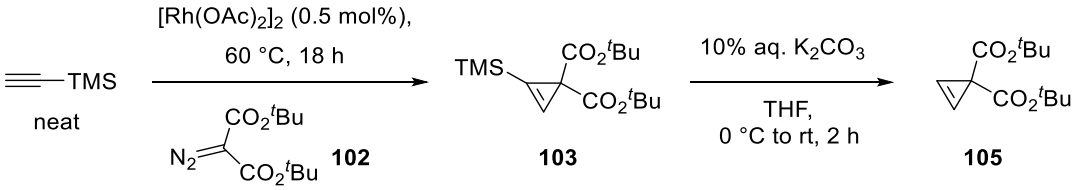


Following a modified literature procedure:[160]

1,8-Diazabicyclo[5.4.0]undec-7-ene (4.91 mL, 32.8 mmol) was added dropwise at 0 °C to a stirring solution of di-*tert*-butyl malonate (5.00 mL, 22.3 mmol, 1.0 equiv) and *p*-acetamidobenzensulfonyl azide (6.44 g, 26.8 mmol, 1.2 equiv) in anhydrous acetonitrile (74 mL). The reaction was warmed to room temperature and stirred for 3 days. The solvent was removed *in vacuo* before trituration with 1:1 diethyl ether/petroleum ether and filtration through a pad of silica. The mixture was concentrated and purified by flash chromatography (100:0 → 90:10 pentane/ethyl acetate) to give di-*tert*-butyl 2-diazomalonate as a light-yellow solid (4.86 g, 90% yield);

R_F 0.41 (90:10 petroleum ether/ethyl acetate); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.51 (s, C*H*$_3$), **^{13}C NMR** ($CDCl_3$, 101 MHz) *δ* 160.5 (R*C*O_2C$(CH_3)_3$), 82.9 (*C*$(CH_3)_3$), 28.4 (*C*H_3) (a signal for the diazo carbon was not observed). All characterisation data is consistent with that reported in the literature.[161]

Di-*tert*-butyl cycloprop-2-ene-1,1-dicarboxylate, 105



Following a modified literature procedure:[86]

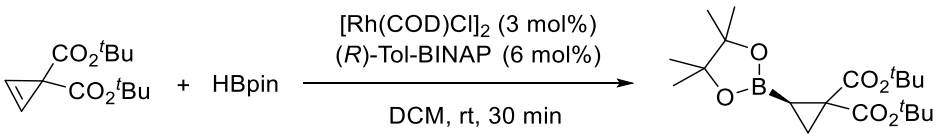
A round bottom flask fitted with a condenser and charged with $Rh_2(OAc)_4$ (66 mg, 0.15 mmol, 0.5 mol%) was evacuated and purged with nitrogen. Trimethylsilyl acetylene (72 mL) was added and the solution was heated to reflux. A solution of di-*tert*-butyl 2-diazomalonate (7.18 g, 29.7 mmol) in trimethylsilyl acetylene (5 mL) was added and the reaction mixture was

maintained at reflux for 4 hours. The solvent was then removed *in vacuo*. At this point, it was beneficial to perform flash column chromatography (100:0 → 90:10 hexane/ethyl acetate) to separate desired intermediate **103** (R_F 0.45 (90:10 petroleum ether/ethyl acetate)) from the more polar impurities. Fractions containing **103** and other non-polar compounds were then transferred to a round bottom flask and the solvent removed *in vacuo* before the addition of THF (150 mL). A solution of 10% aq. K_2CO_3 (56 mL) was added dropwise at 0 °C and the mixture was stirred at room temperature for 2 hours. The phases were separated, and the organic phase was concentrated under reduced pressure. The phases were recombined with the addition of water (150 mL) and diethyl ether (90 mL) and the aqueous phase was extracted with diethyl ether (3 × 90 mL). Combined organic phases were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (100:0 → 80:20 hexane/ethyl acetate) to give **105** as an off-white solid (2.40 g, 34% yield);

R_F 0.29 (90:10 petroleum ether/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 3143, 3099, 2975, 2936, 1721, 1700, 1477, 1457, 1392, 1367; **HRMS** (ESI): Calcd. for $C_{13}H_{20}O_4Na^+$ ($[M+Na]^+$) *m*/*z* 263.1254, found *m*/*z* 263.1265;

^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.88 (s, 2H, *H*C(R)=C(R)*H*), 1.47 (s, 18H, OC(C*H*$_3$)); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 171.0 (R*C*O$_2$C(CH$_3$)$_3$), 103.4 (H*C*(R)=*C*(R)H), 81.3 (O*C*(CH$_3$)), 32.6 (*C*(CO$_2$R)$_2$), 28.2 (OC(*C*H$_3$)).

Di-*tert*-butyl (*R*)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropane-1,1-dicarboxylate, (*R*)-94



105 (*R*)-**94**

Following a modified literature procedure:[86]

A flame dried Schlenk flask was charged with $[Rh(COD)Cl]_2$ (37 mg, 0.075 mmol, 0.03 equiv) and (*R*)-Tol-BINAP (102 mg, 0.150 mmol, 0.06 equiv), evacuated and purged with nitrogen. Anhydrous DCM (2.5 mL) was added and the reaction was stirred for 3 minutes at room temperature. HBpin (0.43 mL, 3.0 mmol, 1.1 equiv) and **105** (0.60 g, 2.5 mmol, 1.0 equiv) were added successively. The mixture was stirred at room temperature for 30 minutes before

filtration through a pad of silica. The crude mixture was concentrated under reduced pressure and added to a pre-equilibrated column with pretroleum ether and eluted within 15 minutes of contact with silica (98:2 → 70:30 hexane/ethyl acetate) to yield (*R*)-**94** as a white waxy solid (0.83 g, 90% yield);

R_F 0.41 (90:10 petroleum ether/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 2981, 2935, 1725, 1473, 1450, 1410, 1367, 1332, 1288, 1233, 1167; **HRMS** (ESI): Calcd. for $C_{19}H_{33}O_6BNa^+$ ($[M+Na]^+$) *m*/*z* 391.2262, found *m*/*z* 391.2282; $[\alpha]_D^{25}$ −45.8 (*c* = 1.95, 97:3 er);

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.47 (s, 9H, OC(CH_3)$_3$), 1.44 (s, 9H, OC(CH_3)$_3$), 1.36 (d, ^3J = 9.5, 2H, CH_2(R)(R')), 1.24 (s, 6H, pinacol CH_3), 1.23 (s, 6H, pinacol CH_3), 0.94 (t, $^3J_{HH}$ = 9.5, 1H, pinB-C*H*(R)(R')); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 170.0 (R*C*O_2C(CH_3)$_3$), 168.2 (R*C*O_2C(CH_3)$_3$), 83.9 (pinacol O*C*(R)(CH_3)$_2$), 81.7 (O*C*(CH_3)$_3$), 81.1 (O*C*(CH_3)$_3$), 36.2 (*C*(R)(R')(CO_2R'')$_2$), 28.2 (OC(*C*H_3)$_3$), 25.1 (pinacol *C*H_3), 24.8 (pinacol *C*H_3), 18.6 (*C*H_2(R)(R')); **^{11}B NMR** ($CDCl_3$, 128 MHz) δ 30.8.

To obtain the racemic sample, (±)-BINAP (6 mol%) was substituted for *R*-Tol-BINAP using the same procedure to yield (±)-**94** in 91% yield.

The enantiopurity of (*R*)-**94** was determined using Pirkle's alcohol ((*R*)-(-)-1-(9-Anthryl)-2,2,2-trifluoroethanol) NMR shift reagent (7.0 equiv, rt, $CDCl_3$, 0.1 M).[89] The spectra are presented in Figure 4.

6.2.2. General procedure A for the oxidation of boronic esters

A round bottom flask containing the boronic ester (0.15 mmol) in THF (1 mL) was cooled to 0 °C. At 0 °C in air, a solution of 2 M NaOH/30% $H_2O_{2(aq)}$ (1.5 mL, 2:1 v/v) was added dropwise. The mixture was stirred at 0 °C for 1 hour and then at room temperature for 1 hour. After this time, water (5 mL) and ethyl acetate (5 mL) were added and the phases separated. The aqueous phase was extracted with ethyl acetate (3 × 5 mL) and the combined organic phases were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (100:0 → 70:30 hexane/ethyl acetate) to give the desired alcohol.

6.2.3. General procedure B for the conversion of alcohols to benzoate esters

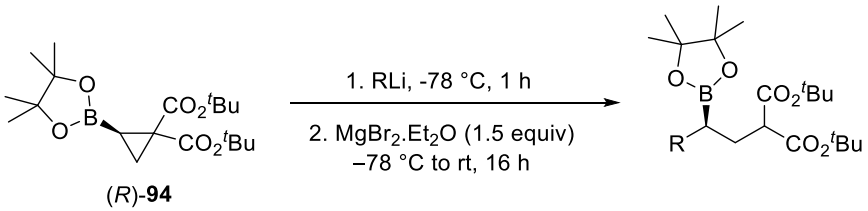
A round bottom flask was charged with the alcohol (1.0 equiv) and DMAP (0.15 equiv) and the flask was evacuated and purged with nitrogen. Anhydrous DCM (0.2 M) was added and

the solution was cooled to 0 °C before the addition of triethylamine (3 equiv) and benzoyl chloride (1.5 equiv). After 20 hours stirring at room temperature (or when TLC analysis showed the reaction had reached completion) water and diethyl ether were added and the aqueous phase was extracted 3 times with diethyl ether. The combined organic phases were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (100:0 → 80:20 hexane/ethyl acetate) to give the desired benzoate ester.

6.2.4. Lewis acid and solvent screen for the 1,2-metallate rearrangement/ring opening of the diactivated n-butylcyclopropyl boronate complex

A flame dried Schlenk flask was charged with **94** (50 mg, 0.14 mmol, 1.0 equiv), evacuated and purged with nitrogen before the addition of anhydrous THF (1 mL). The reaction flask was cooled to −78 °C before the dropwise addition of *n*-butyllithium (0.09 mL, 1.6 M solution in hexane, 1.1 equiv). The reaction was then stirred at −78 °C for 1 hour. After boronate formation, activation conditions were employed, and the reaction was stirred for 16 h. After this time, the crude mixture was then oxidised according to general procedure A and a crude quantitative ^{1}H NMR spectrum was recorded to determine the NMR yield of the desired product.

6.2.5. General procedure C for the boronate formation and subsequent 1,2-metallate rearrangement/ring opening reaction of (*R*)-94



(*R*)-**94**

Boronate formation condition i): A flame dried Schlenk flask was charged with (*R*)-**94** (50 mg, 0.14 mmol, 1.0 equiv), evacuated and purged with nitrogen before the addition of anhydrous THF (1 mL). The reaction flask was cooled to −78 °C before the dropwise addition of the corresponding organolithium reagent (1.1-1.2 equiv). The reaction was then stirred at −78 °C for 1 hour.

Boronate formation condition ii): The organolithium reagent was formed in a flame dried Schlenk flask in anhydrous THF (0.5 mL). (*R*)-**94** (50 mg, 0.14 mmol, 1.0 equiv) was weighed into a vial which was evacuated and purged with nitrogen before the addition of anhydrous THF (0.3 mL). This solution was added dropwise to the Schlenk flask containing the solution

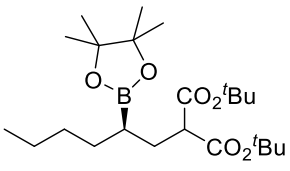
of organolithium reagent cooled to −78 °C. Additional anhydrous THF (2 × 0.2 mL) was used to wash residual (*R*)-**94** from the vial into the reaction mixture. The reaction was then stirred at −78 °C for 1 hour.

Boronate formation condition iii): A flame dried Schlenk flask was charged with (*R*)-**94** (0.050 g, 0.14 mmol, 1.0 equiv) and vinyl/aryl halide (0.163 mmol, 1.2 equiv) then evacuated and purged with nitrogen before the addition of anhydrous THF (1 mL). The reaction flask was cooled to at −78 °C before the dropwise addition of *t*-butyllithium (0.20 mL, 1.6 M in pentane, 2.4 equiv). The reaction was then stirred at −78 °C for 1 hour.

After boronate formation, $MgBr_2.Et_2O$ (53 mg, 0.20 mmol, 1.5 equiv) was added as a solid under a positive flow of nitrogen at −78 °C and the reaction stirred overnight whilst warming slowly to room temperature. Water (10 mL) and diethyl ether (10 mL) were added and the phases separated. The aqueous phase was extracted with diethyl ether (3 × 10 mL) and the combined organic phases were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. A quantitative ^{1}H NMR spectrum of the crude reaction mixture was recorded to determine the NMR yield. The crude reaction mixture was then concentrated and added to a pre-equilibrated column (98:2 pentane/ethyl acetate, 10 g Biotage ZIP cartridge) with petroleum ether (2 × 0.5 mL) and eluted within 10 minutes of contact with silica (98:2 → 80:20 pentane/ethyl acetate) to limit the protodeboronation of product boronic esters.

6.2.6. Reaction scope for the two-component reaction

Di-*tert*-butyl (*R*)-2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexyl)malonate, 110a



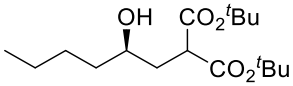
General procedure C, boronate formation condition i): using **(*R*)-94** (56 mg, 0.15 mmol, 1.0 equiv), *n*-butyllithium (0.11 mL, 1.6 M solution in hexane, 1.1 equiv), $MgBr_2.Et_2O$ (59 mg, 0.23 mmol, 1.5 equiv), to yield **110a** as a colourless oil (68 mg, 96% yield).

R_F 0.54 (90:10 petroleum ether/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 2978, 2930, 2873, 1744, 1726, 1457, 1368, 1316, 1251, 1137; **HRMS** (ESI): Calcd. for $C_{23}H_{43}BO_6Na^+$ ([M+Na]$^+$) *m*/*z* 449.3045, found *m*/*z* 449.3044; $[\alpha]_D^{25}$ −13.8 (*c* = 1.92, 97:3 er);

^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.24 (dd, $^3J_{HH}$ = 8.8, 6.9, C*H*(CO$_2$R)$_2$), 1.85 (m, 2H, C*H*$_2$CH(CO$_2$R)$_2$)), 1.44 (s, 9H, CO$_2$C(C*H*$_3$)$_3$), 1.44 (s, 9H, CO$_2$C(C*H*$_3$)$_3$), 1.41 – 1.34 (m, 2H, CH$_3$CH$_2$CH$_2$C*H*$_2$), 1.31 – 1.25 (m, 4H, CH$_3$C*H*$_2$C*H*$_2$), 1.23 (s, 12H, pinacol C*H*$_3$), 0.94 (m, 1H, C*H*(Bpin)), 0.86 (t, $^3J_{HH}$ = 6.0, 3H, C*H*$_3$CH$_2$CH$_2$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 169.4

(R*C*O$_2$C(CH$_3$)$_3$), 169.2 (R*C*O$_2$C(CH$_3$)$_3$), 83.1 (pinacol O*C*(R)(CH$_3$)$_2$), 81.1 (O*C*(CH$_3$)$_3$), 81.1 (O*C*(CH$_3$)$_3$), 53.4 (*C*H(CO$_2$R)$_2$), 31.2 (CH$_3$CH$_2$CH$_2$*C*H$_2$), 30.9 (CH*C*H$_2$CH(Bpin)), 29.9 (*C*H$_2$CH(CO$_2$R)$_2$), 28.1 (OC(*C*H$_3$)$_3$), 25.0 (pinacol *C*H$_3$), 24.8 (pinacol *C*H$_3$), 23.0 (CH$_2$*C*H$_2$CH$_3$), 21.2 (br, *C*H(Bpin)), 14.2 (CH$_2$CH$_2$*C*H$_3$); **^{11}B NMR** (CDCl$_3$, 128 MHz) δ 33.2.

Di-*tert*-butyl (*R*)-2-(2-hydroxyhexyl)malonate, 111a

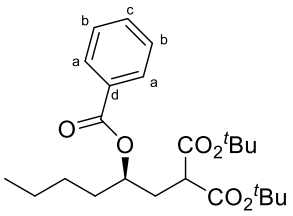


Oxidation of **110a** performed using general procedure A to give **111a** as a colourless oil.

R$_F$ 0.63 (80:20 petroleum ether/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 3449, 2977, 2959, 2931, 2873, 1725, 1456, 1393, 1368, 1251, 1140; **HRMS** (ESI): Calcd. for C$_{17}$H$_{32}$O$_5$Na$^+$ ([M+Na]$^+$) *m*/*z* 339.2142, found *m*/*z* 339.2145; $[\alpha]_D^{25}$ −6.4 (*c* = 1.25, 97:3 er);

^{1}H NMR (CDCl$_3$, 400 MHz) δ 3.63 (m, 1H, C*H*(OH)), 3.41 (dd, $^3J_{HH}$ = 8.0, 6.2, 1H, C*H*(CO$_2$R)$_2$), 2.03 (ddd, $^2J_{HH}$ = 14.4, $^3J_{HH}$ = 8.0, 3.0, 1H, CH(OH)C*H*$_2$CH(CO$_2$R)$_2$), 1.86 (ddd, $^2J_{HH}$ = 14.4, $^3J_{HH}$ = 9.2, 6.2, CH(OH)C*H*$_2$CH(CO$_2$R)$_2$), 1.50 – 1.47 (m, 2H, CH(OH)C*H*$_2$CH$_2$), 1.47 (s, 9H, OC(C*H*$_3$)$_3$)), 1.46 (s, 9H, OC(C*H*$_3$)$_3$)), 1.37 – 1.31 (m, 4H, C*H*$_2$C*H*$_2$CH$_3$), 0.90 (t, $^3J_{HH}$ = 6.9, 3H, CH$_2$C*H*$_3$); **^{13}C NMR** (CDCl$_3$, 101 MHz) δ 169.6 (R*C*O$_2$C(CH$_3$)$_3$), 169.3 (R*C*O$_2$C(CH$_3$)$_3$), 81.7 (O*C*(CH$_3$)$_3$), 70.2 (*C*H(OH)), 51.4 (*C*H(CO$_2$R)$_2$), 37.7 (CH(OH)*C*H-$_2$CH$_2$), 36.2 (CH(OH)*C*H$_2$CH(CO$_2$R)$_2$), 28.07 (OC(*C*H$_3$)$_3$), 28.1 (OC(*C*H$_3$)$_3$), 27.5 (CH$_2$*C*H$_2$CH$_2$), 22.8 (CH$_2$*C*H$_2$CH$_3$), 14.2 (CH$_2$*C*H$_3$).

Di-*tert*-butyl (*R*)-2-(2-(benzoyloxy)hexyl)malonate, 111a'



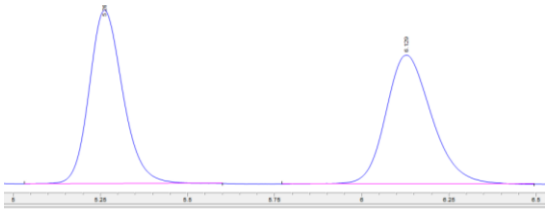
Esterification of **111a** performed using general procedure B to give **111a'** as a colourless oil (70% yield).

R$_F$ 0.59 (90:10 petroleum ether/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 2962, 2931, 2861, 1721, 1452, 1393, 1368, 1259, 1069; **HRMS** (ESI): Calcd. for C$_{24}$H$_{36}$O$_6$Na$^+$ ([M+Na]$^+$) *m*/*z* 443.2404, found *m*/*z* 443.2395; $[\alpha]_D^{25}$ −12.2 (*c* = 0.68, 97:3 er);

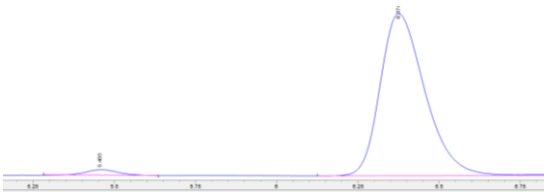
^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.05 (m, 2H, C$_a$*H*), 7.56 (tt, $^3J_{HH}$ = 7.8, $^4J_{HH}$ = 1.4, 1H, C$_c$*H*), 7.45 (t, $^3J_{HH}$ = 7.8, 2H, C$_b$*H*), 5.16 (m, 1H, C*H*(OBz)), 3.31 (dd, $^3J_{HH}$ = 9.4, 5.2, 1H, C*H*(CO$_2$R)$_2$), 2.30 – 2.14 (m, 2H, CH(OBz)C*H*$_2$CH(CO$_2$R)$_2$), 1.62-1.77 (m, 2H, CH(OBz)C*H*$_2$CH$_2$), 1.44 (s, 9H, OC(C*H*$_3$)$_3$), 1.43 (s, 9H, OC(C*H*$_3$)$_3$)), 1.38 – 1.35 (m, 4H, C*H*$_2$C*H*$_2$CH$_3$), 0.89 (t, $^3J_{HH}$ = 7.1, 3H, CH$_2$C*H*$_3$); **^{13}C NMR** (CDCl$_3$, 101 MHz) δ 168.8

(R*C*O$_2$C(CH$_3$)$_3$), 168.6 (R*C*O$_2$C(CH$_3$)$_3$), 166.2 (RO$_2$*C*(Ph)), 132.9 (*C*$_c$H), 130.7 (*C*$_d$H), 129.8 (C$_a$H), 128.4 (*C*$_b$H), 81.8 (O*C*(CH$_3$)$_3$), 72.8 (*C*H(OBz)), 50.7 (*C*H(CO$_2$R)$_2$), 34.5 (CH(OBz)*C*H$_2$CH$_2$), 33.2 (CH(OBz)*C*H$_2$CH(CO$_2$R)$_2$), 28.0 (OC(*C*H$_3$)$_3$), 27.4 (*C*H$_2$CH$_2$CH$_3$), 22.7 (*C*H$_2$CH$_3$), 14.1 (CH$_2$*C*H$_3$).

Enantiomeric ratio of 97:3 was determined using chiral HPLC analysis (Chiralpak IA without guard, 1% IPA/hexane, 1.0 mL/min, 25 °C): t_R = 5.5 [minor, (R)], 6.4 [major, (S)].

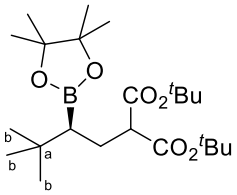


Time	Type	Area	Height	Width	Area%
5.262	VV R	1028.5	152.4	0.1033	49.627
6.129	VB R	1044	113.3	0.139	50.373



Time	Type	Area	Height	Width	Area%
5.455	BB	69.9	9.6	0.0886	2.568
6.374	BV R	2653.5	275.9	0.1462	97.432

Di-*tert*-butyl (*S*)-2-(3,3-dimethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl)malonate, 110b

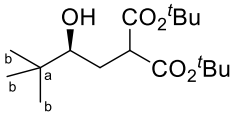


A flame dried Schlenk flask was charged with (*R*)-**94** (74 mg, 0.20 mmol, 1.0 equiv), evacuated and purged with nitrogen before the addition of anhydrous THF (1.5 mL). The reaction flask was cooled to −78 °C before the dropwise addition of *t*-butyllithium (0.15 mL, 1.6 M solution in pentane, 1.2 equiv). The reaction was then stirred at −78 °C for 50 minutes and at room temperature for 5 minutes. After this time, the solvent was removed *in vacuo* and replaced with anhydrous toluene (1.5 mL). After cooling to −78 °C, MgBr$_2$.Et$_2$O (78 mg, 0.30 mmol, 1.5 equiv) was added as a solid under a positive flow of nitrogen and the reaction was stirred overnight whilst warming slowly to room temperature. Water (10 mL) and diethyl ether (10 mL) were added and the phases separated. The aqueous phase was extracted with diethyl ether (3 × 10 mL) and the combined organic phases were washed with brine, dried (MgSO$_4$), filtered and concentrated under reduced pressure. A quantitative ^{1}H NMR spectrum of the crude reaction mixture was recorded to determine the NMR yield. The crude mixture was purified by flash column chromatography (100:0 → 80:20 hexane/ethyl acetate) to give **110b** as an amorphous white solid (32 mg, 38% yield).

R_F 0.35 (90:10 petroleum ether/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 2977, 2871, 1744, 1725, 1474, 1394, 1371, 1313, 1253, 1137; **HRMS** (ESI): Calcd. for $C_{23}H_{43}BO_6Na^+$ ($[M+Na]^+$) *m*/*z* 449.3045, found *m*/*z* 449.3053; $[\alpha]_D^{25}$ −34.4 (*c* = 1.47, 96:4 er);

^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.07 (dd, $^3J_{HH}$ = 11.9, 3.8, 1H, C*H*($CO_2R)_2$), 1.97 (ddd, $^2J_{HH}$ = 12.8, $^3J_{HH}$ = 11.9, 3.3, C*H*$_2$CH($CO_2R)_2$)), 1.82 (dt, $^2J_{HH}$ = 12.8, $^3J_{HH}$ = 12.8, 3.8, 1H, C*H*$_2$CH($CO_2R)_2$)), 1.45 (s, 9H, OC(C*H*$_3$)$_3$), 1.44 (s, 9H, OC(C*H*$_3$)$_3$)), 1.25 (s, 12H, pinacol C*H*$_3$), 0.95 (s, 9H, C$_b$*H*$_3$), 0.78 (dd, $^3J_{HH}$ = 12.8, 3.3, 1H, C*H*(Bpin)); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 169.4 (R*C*O_2C($CH_3)_3$), 169.0 (R*C*O_2C($CH_3)_3$), 83.2 (pinacol O*C*(R)($CH_3)_2$), 81.1 (O*C*($CH_3)_3$), 81.0 (O*C*($CH_3)_3$), 54.2 (*C*H($CO_2R)_2$), 33.7 (br., *C*H(Bpin)), 32.3 (*C*H$_2$CH($CO_2R)_2$), 29.6 (*C*$_b$), 28.1 (OC(*C*$H_3)_3$), 26.4 (*C*$_a$), 25.1 (pinacol *C*H_3), 25.0 (pinacol *C*H_3); **^{11}B NMR** ($CDCl_3$, 128 MHz) δ 32.4.

Di-*tert*-butyl (*S*)-2-(2-hydroxy-3,3-dimethylbutyl)malonate, 111b

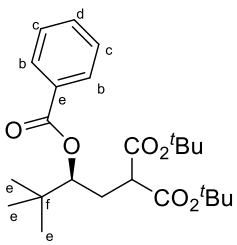


Oxidation of **110b** performed using general procedure A to give **111b** as a colourless oil.

R_F 0.33 (80:20 petroleum ether/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 3485, 2973, 2867, 1724, 1477, 1395, 1372, 1253, 1143; **HRMS** (ESI): Calcd. for $C_{17}H_{32}O_5Na^+$ ($[M+Na]^+$) *m*/*z* 339.2142, found *m*/*z* 339.2139; $[\alpha]_D^{25}$ −25.5 (*c* = 0.63, 96:4 er);

^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.42 (dd, $^3J_{HH}$ = 8.6, 35.7, 1H, C*H*($CO_2R)_2$), 3.22 (ddd, $^3J_{HH}$ = 10.9, 6.2, 2.0, 1H, C*H*(OH)), 2.05 (ddd, $^2J_{HH}$ = 14.3, $^3J_{HH}$ = 8.6, 2.0, C*H*$_2$CH($CO_2R)_2$)), 1.84 (d, $^3J_{HH}$ = 6.2, 1H, CH(O*H*)), 1.79 (ddd, $^2J_{HH}$ = 14.3, $^3J_{HH}$ = 10.9, 5.7, 1H, C*H*$_2$CH($CO_2R)_2$)), 1.46 (s, 9H, OC(C*H*$_3$)$_3$), 1.46 (s, 9H, OC(C*H*$_3$)$_3$)), 0.91 (s, 9H, C$_b$*H*$_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 169.8 (R*C*O_2C($CH_3)_3$), 169.3 (R*C*O_2C($CH_3)_3$), 81.7 (O*C*($CH_3)_3$), 81.6 (O*C*($CH_3)_3$), 77.9 (*C*H(OH)), 52.1 (*C*H($CO_2R)_2$), 35.2 (*C*$_a$), 30.9 (*C*H$_2$CH($CO_2R)_2$), 28.1 (OC(*C*$H_3)_3$), 28.1 (OC(*C*$H_3)_3$), 25.7 (*C*$_b$).

Di-*tert*-butyl (*S*)-2-(2-(benzoyloxy)-3,3-dimethylbutyl)malonate, 111b'



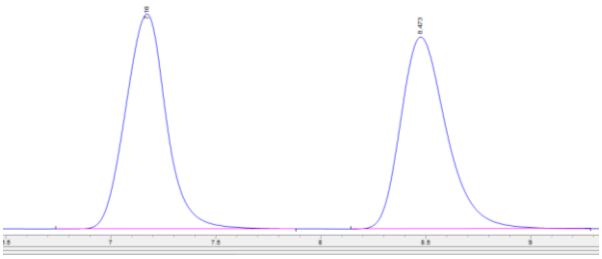
Esterification of **111b** performed using general procedure B to give **111b'** as a colourless oil (66% yield).

R_F 0.41 (90:10 petroleum ether/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 2972, 2930, 1743, 1723, 1484, 1456, 1368, 1271, 1167, 1143; **HRMS** (ESI):

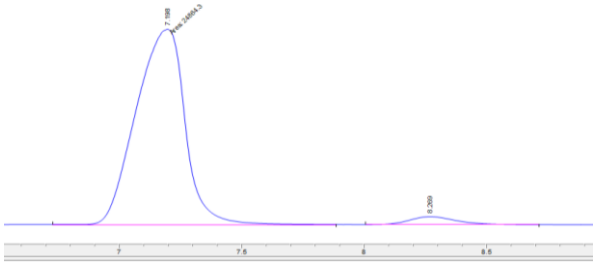
Calcd. for $C_{24}H_{36}O_6Na^+$ ([M+Na]$^+$) *m*/*z* 443.2404, found *m*/*z* 443.2402; $[\alpha]_D^{25}$ −16.5 (*c* = 0.54, (96:4 er);

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.06 (dd, $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.1, 2H, C_aH), 7.56 (tt, $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.1, 1H, C_cH), 7.45 (t, $^3J_{HH}$ = 7.6, 2H, C_bH), 5.03 (dd, $^3J_{HH}$ = 11.3, 2.0, 1H, 1H, C*H*(OBz)), 3.18 (dd, $^3J_{HH}$ = 10.2, 4.2, 1H, C*H*($CO_2R)_2$), 2.31 (ddd, $^2J_{HH}$ = 14.5, $^3J_{HH}$ = 10.2, 2.0, 1H, CH_2CH($CO_2R)_2$), 2.07 (ddd, $^2J_{HH}$ = 14.5, $^3J_{HH}$ = 11.3, 4.2, 1H, CH_2CH($CO_2R)_2$), 1.48 (s, 9H, OC(C$H_3)_3$), 1.36 (s, 9H, OC(C$H_3)_3$)), 1.00 (s, 9H, C_eH_3); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 169.0 (R*C*O_2C($CH_3)_3$), 168.4 (R*C*O_2C($CH_3)_3$), 166.2 (RO_2C(Ph)), 132.9 (C_cH), 130.5 (C_dH), 129.8 (C_aH), 128.4 (C_bH), 81.7 (O*C*($CH_3)_3$), 81.7 (O*C*($CH_3)_3$), 79.0 (*C*H(OBz)), 51.0 (*C*H($CO_2R)_2$), 35.3 (C_f), 29.1 (*C*H_2CH($CO_2R)_2$), 28.0 (OC(*C*$H_3)_3$), 27.9 (OC(*C*$H_3)_3$), 26.0 (C_e).

Enantiomeric ratio of 96:4 was determined using chiral HPLC (Chiralpak IC with guard, 0.5% IPA/hexane, 1.0 mL/min, 25 °C): t_R = 7.20 [major, (S)], 8.27 [minor, (R)].

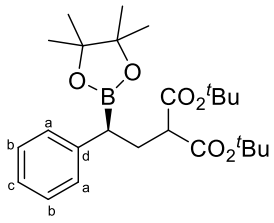


Time	Type	Area	Height	Width	Area%
7.169	VV R	13007.7	963.6	0.197	49.887
8.473	BV R	13066.4	860.5	0.2292	50.113



Time	Type	Area	Height	Width	Area%
7.198	MM	24864.3	1769.9	0.2341	96.358
8.269	VV R	939.8	71.4	0.157	3.642

Di-*tert*-butyl (*S*)-2-(2-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)malonate, 110c



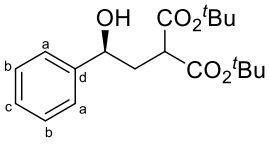
General procedure C, boronate formation condition i), using (*R*)-**94** (50 mg, 0.14 mmol, 1.0 equiv), phenyllithium (0.08 mL, 1.9 M solution in dibutylether, 1.15 equiv), $MgBr_2{\cdot}Et_2O$ (53 mg, 0.20 mmol, 1.5 equiv), to yield **110c** as a white solid (47 mg, 78% yield).

Performed using the same procedure on a 1 mmol scale using (*R*)-**94** (0.402 g, 1.09 mmol, 1.0 equiv), phenyllithium (0.69 mL, 1.9 M solution in dibutylether, 1.2 equiv), $MgBr_2{\cdot}Et_2O$ (0.422 g, 1.64 mmol, 1.5 equiv), to yield **110c** as a white solid (0.431 g, 88% yield).

R_F 0.41 (90:10 petroleum ether/ethyl acetate); IR (film) ν_{max}/cm^{-1}: 2977, 2932, 1741(C=O), 1724, 1453, 1367, 1323, 1254, 1140; **HRMS** (ESI): Calcd. for $C_{25}H_{39}BO_6Na^+$ ([M+Na]$^+$) *m*/*z* 469.2732, found *m*/*z* 469.2730; $[\alpha]_D^{25}$ 20.0 (*c* = 2.25, 97:3 er);

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.27 – 7.12 (m, 5H, ArC*H*), 3.06 (m, 1H, C*H*($CO_2R)_2$), 2.36 – 2.11 (m, 3H, C*H*(Ph)(Bpin), $CH_2CH(CO_2R)_2$), 1.46 (s, 9H, OC($CH_3)_3$), 1.41 (s, 9H, OC($CH_3)_3$), 1.20 (s, 6H, pinacol CH_3), 1.17 (s, 6H, pinacol CH_3); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 169.2 ($RCO_2C(CH_3)_3$), 169.0 ($RCO_2C(CH_3)_3$), 141.9 (C_d), 128.8 (C_a), 128.6 (C_b), 125.7 (C_c), 83.6 (pinacol O*C*(R)($CH_3)_2$), 81.3 (O*C*($CH_3)_3$), 81.2 (O*C*($CH_3)_3$), 52.8 (*C*H($CO_2R)_2$), 31.3 ($CH_2CH(CO_2R)_2$), 28.1 (OC(*C*$H_3)_3$), 28.1 (OC(*C*$H_3)_3$), 24.8 (pinacol *C*H_3), 24.7 (pinacol *C*H_3); **^{11}B NMR** ($CDCl_3$, 128 MHz) δ 32.3.

Di-*tert*-butyl (*S*)-2-(2-hydroxy-2-phenylethyl)malonate, 111c

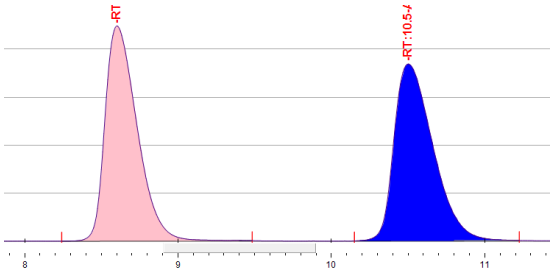


Oxidation of **110c** (0.372 g, 0.835 mmol) performed using general procedure A to give **111c** as a white solid (0.270 g, 96% yield).

R_F 0.36 (80:20 petroleum ether/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 3452 (O-H), 2978, 2934, 1716, 1456, 1368, 1256, 1142; **HRMS** (ESI): Calcd. for $C_{19}H_{28}O_5Na^+$ *m/z* 359.1829, found *m/z* 359.1843 $[M+Na]^+$; $[\alpha]_D^{25}$ −16.6 (*c* = 1.38, 97:3 er);

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28 – 7.15 (m, 5H, ArC*H*), 4.67 (br. dt, $^3J_{HH}$ = 3.9, 6.7, 1H, C*H*OH), 3.28 (t, $^3J_{HH}$ = 7.1, 1H, C*H*($CO_2R)_2$), 2.34 (br. d, $^3J_{HH}$ = 3.9, 1H, O*H*), 2.15 – 2.12 (m, 2H, $CH_2CH(CO_2R)_2$), 1.37 (s, 9H, OC($CH_3)_3$), 1.36 (s, 9H, OC($CH_3)_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 169.2 ($RCO_2C(CH_3)_3$), 169.1 ($RCO_2C(CH_3)_3$), 144.1 (C_d), 128.7 (C_b), 127.8 (C_c), 125.9 (C_a), 81.8 (O*C*($CH_3)_3$), 72.4 (*C*HOH), 51.4 (*C*H($CO_2R)_2$), 38.0 ($CH_2CH(CO_2R)_2$), 28.1 (OC(*C*$H_3)_3$), 28.1 (OC(*C*$H_3)_3$).

Enantiomeric ratio of 97:3 was determined using chiral SFC analysis (Whelk 01 column, 10% IPA/hexane – iso 10%, 4 mL/min, 125 bar): t_R = 8.6 [major, (S)], 10.7 [minor, (R)].



Area Percent	Area	Retention Time	Height
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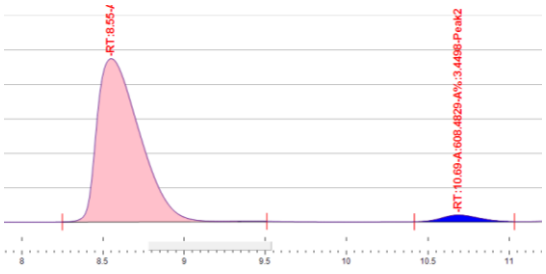
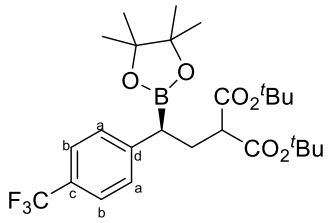
49.9433	6412.5107	10.5 min	367.8773



Area Percent	Area	Retention Time	Height
96.5502	17029.8751	8.55 min	947.1715
3.4498	608.4829	10.69 min	39.265

Di-*tert*-butyl (*S*)-2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(4-(trifluoromethyl)phenyl)ethyl)malonate, 110d



General procedure C, boronate formation condition ii), 4-trifluoromethylphenyllithium was synthesised according to the following procedure:

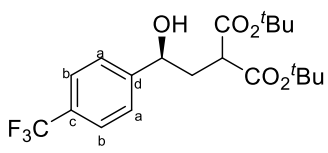
1-Bromo-4-(trifluoromethyl)benzene (21 µL, 0.15 mmol, 1.1 equiv) was added to a flame dried Schlenk flask and dissolved in anhydrous THF (0.5 mL) then cooled to −78 °C. *n*-Butyllithium (93 µL, 1.6 M solution in hexane, 1.1 equiv) was added and the reaction stirred at −78 °C for 1 hour.

Using (*R*)-**94** (50 mg, 0.14 mmol, 1.0 equiv), 4-trifluoromethylphenyllithium (1.1 equiv), $MgBr_2 \cdot Et_2O$ (53 mg, 0.20 mmol, 1.5 equiv), to yield **110d** as an amorphous white solid (43 mg, 62% yield).

R_F 0.38 (90:10 petroleum ether/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 2981, 2937, 1740 (C=O), 1718, 1617, 1478, 1444, 1368, 1324, 1247; **HRMS** (ESI): Calcd. for $C_{26}H_{38}BF_3O_6Na^+$ ($[M+Na]^+$) *m*/*z* 537.2606, found *m*/*z* 537.2612; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ 15.6 (*c* = 2.11, 97:3 er);

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.51 (d, $^3J_{HH}$ = 8.2, 2H, C_bH), 7.29 (d, $^3J_{HH}$ = 8.2, 2H, C_aH), 3.02 (m, 1H, $CH(CO_2R)_2$), 2.41 – 2.31 (m, 2H, CH(Ar)(Bpin), $CH_2CH(CO_2R)_2$), 2.22 – 2.13 (m, 1H, $CH_2CH(CO_2R)_2$), 1.46 (s, 9H, $OC(CH_3)_3$), 1.41 (s, 9H, $OC(CH_3)_3$), 1.20 (s, 6H, pinacol CH_3), 1.18 (s, 6H, pinacol CH_3); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 169.0 ($RCO_2C(CH_3)_3$), 168.8 ($RCO_2C(CH_3)_3$), 146.3 (C_d), 129.0 (C_a), 128.0 (q, $^2J_{CF}$ = 32, C_c), 125.5 (q, $^3J_{CF}$ = 4, C_b), 124.3 (q, $^1J_{CF}$ = 272, CF_3), 83.9 (pinacol $OC(R)(CH_3)_2$), 81.6 ($OC(CH_3)_3$), 81.5 ($OC(CH_3)_3$), 52.7 ($CH(CO_2R)_2$), 30.9 ($CH_2CH(CO_2R)_2$), 29.8 (CH(Bpin)), 28.1 ($OC(CH_3)_3$), 28.0 ($OC(CH_3)_3$), 24.7 (pinacol CH_3), 24.7 (pinacol CH_3); **^{11}B NMR** ($CDCl_3$, 128 MHz) δ 31.8; **^{19}F NMR** ($CDCl_3$, 377 MHz) δ −62.29 (s, CF_3).

Di-*tert*-butyl (*S*)-2-(2-hydroxy-2-(4-(trifluoromethyl)phenyl)ethyl)malonate, 111d

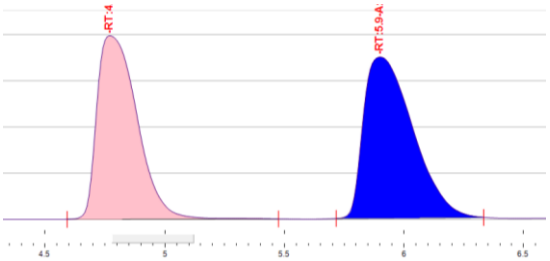


Oxidation of **110d** performed using general procedure A to give **111d** as a colourless oil.

R_F 0.39 (80:20 petroleum ether/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 3457, 2979, 2935, 1724, 1394, 1324, 1255, 1161, 1125; **HRMS** (ESI): Calcd. for $C_{20}H_{27}F_3O_5$ *m*/*z* 427.1703, found *m*/*z* 427.1708 $[M+Na]^+$; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ −11.4 (*c* = 0.96, 97:3 er);

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.59 (d, $^{3}J_{HH}$ = 8.2, 2H, C_bH), 7.48 (d, $^{3}J_{HH}$ = 8.2, 2H, C_aH), 4.85 (br. m, 1H, C*H*OH), 3.37 (dd, $^{3}J_{HH}$ = 6.3, 7.9, 1H, C*H*($CO_2R)_2$), 2.75 (br. d, 1H, O*H*), 2.28 – 2.14 (m, 2H, CH_2CH($CO_2R)_2$), 1.45 (s, 9H, OC($CH_3)_3$), 1.45 (s, 9H, OC($CH_3)_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 169.0 (R*C*O_2C($CH_3)_3$), 148.1 (C_d), 169.0 (R*C*O_2C($CH_3)_3$), 129.9 (q, $^{2}J_{CF}$ = 32, C_c), 126.1 (C_a), 125.5 (q, $^{3}J_{CF}$ = 4, C_b), 124.1 (q, $^{1}J_{CF}$ = 272, *C*F_3), 82.1 (O*C*($CH_3)_3$), 82.0 (O*C*($CH_3)_3$), 71.7 (*C*HOH), 51.2 (*C*H($CO_2R)_2$), 38.0 (CH_2*C*H($CO_2R)_2$), 28.0 (OC(*C*$H_3)_3$), 28.0 (OC(*C*$H_3)_3$); **^{19}F NMR** ($CDCl_3$, 377 MHz) δ −62.39 (s, C*F*$_3$).

Enantiomeric ratio of 97:3 was determined using chiral SFC analysis (Whelk 01 column, 10% IPA/hexane – iso 10%, 4 mL/min, 125 bar): t_R = 4.9 [major, (S)], 6.1 [minor, (R)].



Area Percent	Area	Retention Time	Height
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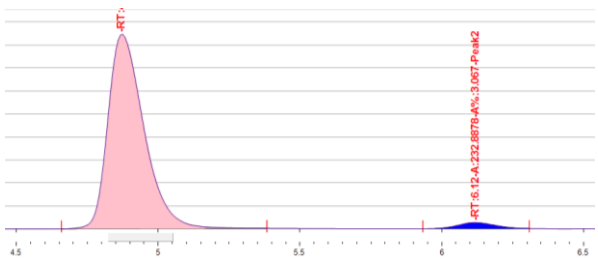
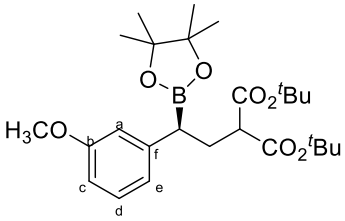
51.7808	24571.5262	5.9 min	1740.1016



Area Percent	Area	Retention Time	Height
96.933	7360.3563	4.87 min	845.6166
3.067	232.8878	6.12 min	26.2097

Di-*tert*-butyl (*S*)-2-(2-(3-methoxyphenyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)malonate, 110e



General procedure C, boronate formation condition ii), 3-methoxyphenyllithium was synthesised according to the following procedure:

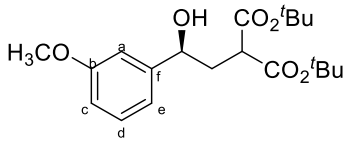
3-Bromoanisole (22 µL, 0.17 mmol, 1.2 equiv) was added to a flame dried Schlenk flask and dissolved in anhydrous THF (0.5 mL) then cooled to −78 °C. *n*-Butyllithium (0.11 mL, 1.6 M solution in hexane, 1.2 equiv) was added and the reaction stirred at −78 °C for 1 hour.

Using (*R*)-**94** (53 mg, 0.15 mmol, 1.0 equiv), 3-methoxyphenyllithium (1.2 equiv), $MgBr_2.Et_2O$ (56 mg, 0.22 mmol, 1.5 equiv), to yield **110e** as a colourless oil (53 mg, 77% yield).

R_F 0.27 (90:10 petroleum ether/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 2977, 2932, 1740, 1724, 1598, 1582, 1486, 1455, 1367, 1323, 1256; **HRMS** (ESI): Calcd. for $C_{26}H_{41}BO_7Na^+$ ([M+Na]$^+$) *m*/*z* 499.2838, found *m*/*z* 499.2847; $[\alpha]_D^{25}$ 21.0 (c = 1.89, 97:3 er);

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.16 (dd, $^3J_{HH}$ = 8.0, 7.4, 1H, C_dH) 6.77 (dt, $^3J_{HH}$ = 7.4, $^4J_{HH}$ =1.2, 1H, C_eH), 6.73 (t, $^4J_{HH}$ = 2.0, 1H, C_aH), 6.69 (ddd, $^3J_{HH}$ = 8.0, $^4J_{HH}$ = 2.6, 0.9, 1H, C_cH), 3.78 (s, 3H, OCH_3), 3.08 (m, 1H, $CH(CO_2R)_2$), 2.34 – 2.27 (m, 2H, CH(Ar)(Bpin), $CH_2CH(CO_2R)_2$), 2.19 – 2.10 (m, 1H, $CH_2CH(CO_2R)_2$), 1.46 (s, 9H, $OC(CH_3)_3$), 1.42 (s, 9H, $OC(CH_3)_3$), 1.21 (s, 6H, pinacol CH_3), 1.18 (s, 6H, pinacol CH_3); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 169.2 ($RCO_2C(CH_3)_3$), 168.9 ($RCO_2C(CH_3)_3$), 159.8 (C_b), 143.5 (C_f), 129.4 (C_d), 121.3 (C_e), 114.3 (C_a), 111.5 (C_c), 83.6 (pinacol $OC(R)(CH_3)_2$), 81.3 ($OC(CH_3)_3$), 81.2 ($OC(CH_3)_3$), 55.2 (OCH_3), 52.7 ($CH(CO_2R)_2$), 31.3 ($CH_2CH(CO_2R)_2$), 28.1 ($OC(CH_3)_3$), 28.1 ($OC(CH_3)_3$), 24.8 (pinacol CH_3), 24.7 (pinacol CH_3); **^{11}B NMR** ($CDCl_3$, 128 MHz) δ 31.8.

Di-*tert*-butyl (*S*)-2-(2-hydroxy-2-(3-methoxyphenyl)ethyl)malonate, 111e

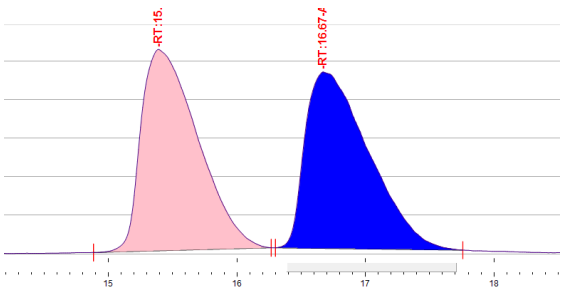


Oxidation of **110e** performed using general procedure A to give **111e** as a colourless oil.

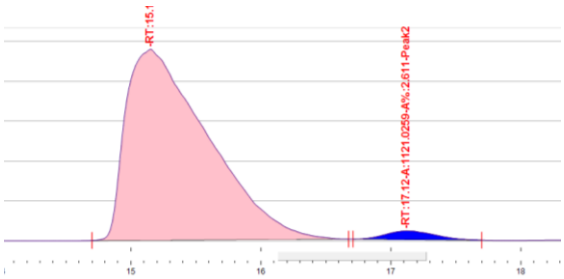
R_F 0.29 (80:20 petroleum ether/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 3453, 2977, 2931, 1716, 1602, 1457, 1368, 1257, 1141; **HRMS** (ESI): Calcd. for $C_{20}H_{30}O_6Na^+$ *m*/*z* 389.1935, found *m*/*z* 389.1936 $[M+Na]^+$; $[\alpha]_D^{25}$ −12.0 (*c* = 1.05, 97:3 er);

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.26 (t, $^3J_{HH}$ = 8.2, 1H, C_dH), 6.77 (ddd, $^3J_{HH}$ = 7.6, 1.2, 0.9, 1H, C_eH), 6.93 (m, 2H, C_aH, C_eH), 6.81 (ddd, $^3J_{HH}$ = 8.2, $^4J_{HH}$ = 2.5, 1.0, 1H, C_cH), 4.75 (t, $^3J_{HH}$ = 6.6, 1H, O*H*), 3.81 (s, 3H, OCH_3), 3.38 (t, $^3J_{HH}$ = 7.2, 1H, $CH(CO_2R)_2$), 2.44 (br, 1H, O*H*), 2.25 – 2.21 (m, 2H, $CH_2CH(CO_2R)_2$), 1.47 (s, 9H, $OC(CH_3)_3$), 1.46 (s, 9H, $OC(CH_3)_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 169.2 ($RCO_2C(CH_3)_3$), 169.1 ($RCO_2C(CH_3)_3$), 160.0 (C_b), 145.8 (C_f), 129.7 (C_d), 118.1 (C_e), 113.4 (C_a), 111.2 (C_c), 81.8 ($OC(CH_3)_3$), 72.3 (*C*HOH), 55.4 (OCH_3), 51.4 ($CH(CO_2R)_2$), 38.0 ($CH_2CH(CO_2R)_2$), 28.1 ($OC(CH_3)_3$), 28.1 ($OC(CH_3)_3$).

Enantiomeric ratio of 97:3 was determined using chiral SFC analysis (Whelk 01 column, 10% IPA/hexane – iso 10%, 4 mL/min, 125 bar): t_R = 15.2 [major, (S)], 17.1 [minor, (R)].

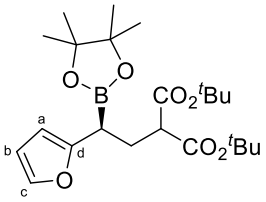


Area Percent	Area	Retention Time	Height
50.4154	15932.8404	15.39 min	522.9043
49.5846	15670.2585	16.67 min	458.0018



Area Percent	Area	Retention Time	Height
97.389	41813.3521	15.15 min	956.9196
2.611	1121.0259	17.12 min	43.6785

Di-*tert*-butyl (*S*)-2-(2-(furan-2-yl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)malonate, 110f



General procedure C, boronate formation condition ii), furan-2-yllithium was synthesised according to the following procedure:

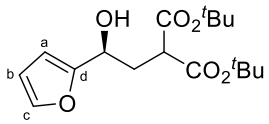
Furan (12 µL, 0.16 mmol, 1.2 equiv) was added to a flame dried Schlenk flask cooled to −78 °C followed by anhydrous THF (0.5 mL). *n*-Butyllithium (0.10 mL, 1.6 M solution in hexane, 1.2 equiv) was added and the reaction warmed to room temperature and stirred for 30 minutes.

Using (*R*)-**94** (50 mg, 0.14 mmol, 1.0 equiv), furan-2-yllithium (1.2 equiv), $MgBr_2 \cdot Et_2O$ (53 mg, 0.20 mmol, 1.5 equiv), to yield **110f** as a colourless oil (43 mg, 73% yield).

R_F 0.32 (90:10 petroleum ether/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 2978, 2933, 1741, 1725, 1586, 1504, 1457, 1367, 1330, 1249; **HRMS** (ESI): Calcd. for $C_{23}H_{37}BO_7Na^+$ ($[M+Na]^+$) *m*/*z* 459.2525, found *m*/z 459.2541; $[\alpha]_D^{25}$ 18.0 (c = 1.57, 96:4 er);

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28 (dd, $^3J_{HH}$ = 1.9, $^4J_{HH}$ = 0.8, 1H, C_cH), 6.25 (dd, $^3J_{HH}$ = 3.1, 1.9, 1H, C_bH), 6.01 (dt, $^3J_{HH}$ = 3.1, $^4J_{HH}$ = 0.8, 1H, C_aH), 3.16 (dd, $^3J_{HH}$ = 8.5, 6.8, 1H, $CH(CO_2R)_2$), 2.49 (dd, $^3J_{HH}$ = 9.4, 7.0, 1H, CH(Bpin)), 2.27 – 2.13 (m, 2H, $CH_2CH(CO_2R)_2$), 1.45 (s, 9H, $OC(CH_3)_3$), 1.43 (s, 9H, $OC(CH_3)_3$), 1.24 (s, 6H, pinacol CH_3), 1.23 (s, 6H, pinacol CH_3); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 169.0 ($RCO_2C(CH_3)_3$), 168.8 ($RCO_2C(CH_3)_3$), 155.4 (C_d), 141.2 (C_c), 110.3 (C_b), 105.7 (C_a), 83.9 (pinacol OC(R)$(CH_3)_2$), 81.4 ($OC(CH_3)_3$), 81.3 ($OC(CH_3)_3$), 52.9 ($CH(CO_2R)_2$), 29.0 ($CH_2CH(CO_2R)$), 28.1 ($OC(CH_3)_3$), 28.1 ($OC(CH_3)_3$), 24.9 (pinacol CH_3), 24.1 (pinacol CH_3), 22.7 (br, CH(Bpin)); **^{11}B NMR** ($CDCl_3$, 128 MHz) δ 31.8.

Di-*tert*-butyl (*S*)-2-(2-(furan-2-yl)-2-hydroxyethyl)malonate, 111f

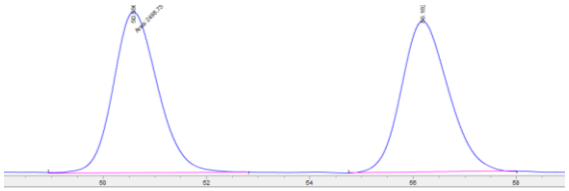


Oxidation of **110f** performed using general procedure A to give **111f** as a colourless oil.

R_F 0.30 (80:20 petroleum ether/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 3447, 2778, 2933, 1722, 1368, 1252, 1140; **HRMS** (ESI): Calcd. for $C_{17}H_{26}O_6Na^+$ *m/z* 349.1622, found *m*/z 349.1624 $[M+Na]^+$; $[\alpha]_D^{25}$ −15.4 (c = 0.45, 96:4 er);

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37 (dd, $^3J_{HH}$ = 1.8, $^4J_{HH}$ = 0.7, 1H, C_cH), 6.32 (dd, $^3J_{HH}$ = 3.3, 1.8, 1H, C_bH), 6.26 (dt, $^3J_{HH}$ = 3.3, $^4J_{HH}$ = 0.7, 1H, C_aH), 4.77 (br. dd, $^3J_{HH}$ = 12.0, 6.1, 1H, C*H*OH), 3.40 (t, $^3J_{HH}$ = 7.1, 1H, C*H*$(CO_2R)_2$), 2.40 (br. d, $^3J_{HH}$ = 5.5, 1H, O*H*), 2.37 – 2.33 (m, 2H, $CH_2CH(CO_2R)_2$), 1.46 (s, 9H, $OC(CH_3)_3$), 1.46 (s, 9H, $OC(CH_3)_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 169.1 ($RCO_2C(CH_3)_3$), 169.0 ($RCO_2C(CH_3)_3$), 156.0 (C_d), 141.3 (C_c), 110.3 (C_b), 106.2 (C_a), 82.0 ($OC(CH_3)_3$), 81.9 ($OC(CH_3)_3$), 66.1 (*C*HOH), 51.0 (*C*H$(CO_2R)_2$), 34.5 ($CH_2CH(CO_2R)$), 28.1 ($OC(CH_3)_3$).

Enantiomeric ratio of 96:4 was determined using chiral HPLC analysis (Chiralpak IA with guard, 1% IPA/hexane, 0.5 mL/min, 25 °C): t_R = 51.3 [major, (S)], 57.8 [minor, (R)].



Time	Type	Area	Height	Width	Area%
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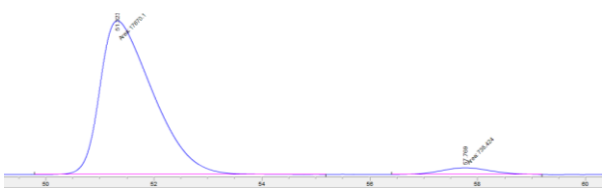
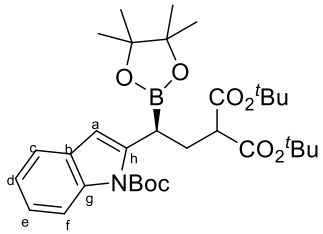
56.182	BB	2490.8	39.2	0.7481	49.920



Time	Type	Area	Height	Width	Area%
51.323	MM	17670.1	260.2	1.132	96.004
57.769	PP	735.4	11.4	1.0757	3.996

Di-*tert*-butyl 2-(2-(1-(*tert*-butoxycarbonyl)-1H-indol-2-yl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)malonate, 110g



General procedure C, boronate formation condition ii), (*N*-Boc-indol-2-yl)lithium was synthesised according to the following procedure:

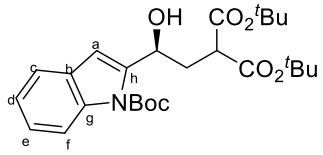
N-Boc-indole (35 µL, 0.16 mmol, 1.2 equiv) was added to a flame dried Schlenk flask and dissolved in anhydrous THF (0.5 mL) then cooled to −78 °C. *n*-Butyllithium (0.10 mL, 1.6 M solution in hexane, 1.2 equiv) was added dropwise and the reaction stirred at −78 °C for 1 hour.

Using (*R*)-**94** (50 mg, 0.14 mmol, 1.0 equiv), (*N*-Boc-indol-2-yl)lithium (1.2 equiv), $MgBr_2 \cdot Et_2O$ (53 mg, 0.20 mmol, 1.5 equiv), to yield **110g** as a colourless oil (24 mg, 30% yield).

R_F 0.25 (90:10 petroleum ether/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 2978, 2933, 1720, 1454, 1368, 1332, 1295, 1254, 1156, 1139; **HRMS** (ESI): Calcd. for $C_{32}H_{48}BNO_8Na^+$ ($[M+Na]^+$) *m*/*z* 608.3365, found *m*/*z* 608.3348; $[\alpha]_D^{25}$ 63.5 (c = 1.09, 97:3 er);

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.94 (m, 1H, C_fH), 7.42 (m, 1H, C_cH), 7.17 (m, 2H, C_dH/C_eH), 6.34 (s, 1H, C_aH), 3.25 (dd, $^3J_{HH}$ = 8.9, 5.9, 1H, $CH(CO_2R)_2$), 2.72 (dd, $^3J_{HH}$ = 10.1, 5.4, 1H, CH(Ar)(Bpin)), 2.43 (ddd, $^2J_{HH}$ = 14.7, $^3J_{HH}$ = 8.9, 5.4, 1H, $CH_2CH(CO_2R)_2$), 2.27 (ddd, $^2J_{HH}$ = 14.7, $^3J_{HH}$ = 10.1, 5.9, 1H, $CH_2CH(CO_2R)_2$), 1.68 (s, 9H, Boc $OC(CH_3)_3$), 1.45 (s, 9H, $OC(CH_3)_3$), 1.37 (s, 9H, $OC(CH_3)_3$), 1.24 (s, 6H, pinacol CH_3), 1.22 (s, 6H, pinacol CH_3); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 169.3 ($RCO_2C(CH_3)_3$), 169.2 ($RCO_2C(CH_3)_3$), 151.1 ($NCO_2C(CH_3)_3$), 142.6 (C_h), 136.2 (C_g), 130.0 (C_b), 123.0 (C_d), 122.6 (C_e), 120.0 (C_c), 115.9 (C_f), 108.8 (C_a), 84.0 (Boc $OC(CH_3)_3$), 83.4 (pinacol $OC(R)(CH_3)_2$), 81.2 ($OC(CH_3)_3$), 81.1 ($OC(CH_3)_3$), 52.9 ($CH(CO_2R)_2$), 28.6 ($CH_2CH(CO_2R)_2$), 28.5 (Boc $OC(CH_3)_3$), 28.1 ($OC(CH_3)_3$), 28.0 ($OC(CH_3)_3$), 25.1 (pinacol CH_3), 25.0 (pinacol CH_3); **^{11}B NMR** ($CDCl_3$, 128 MHz) δ 30.8.

Di-*tert*-butyl (*S*)-2-(2-(1-(*tert*-butoxycarbonyl)-1H-indol-2-yl)-2-hydroxyethyl)malonate, 111g



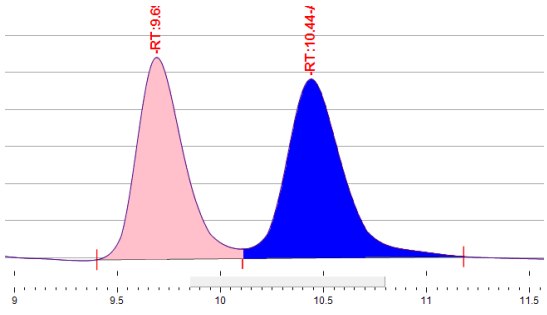
Oxidation of **110g** performed using general procedure A to give **111g** as a colourless oil.

R_F 0.28 (80:20 petroleum ether/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 3495, 2978, 2933, 1729, 1454, 1370, 1331, 1253, 1161; **HRMS** (ESI): Calcd. for $C_{26}H_{37}NO_7Na^+$ ($[M+Na]^+$) *m*/*z* 498.2462, found *m*/*z* 498.2470; $[\alpha]_D^{25}$ −4.0 (c = 0.62, 97:3 er);

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.97 (m, 1H, C_fH), 7.50 (m, 1H, C_cH), 7.27 (dt, , $^3J_{HH}$ = 7.3, $^4J_{HH}$ = 1.4, 1H, C_eH), 7.21 (dt, $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.2, 1H, C_dH), 5.08 (dt, $^3J_{HH}$ = 8.3, 5.5, 1H, $CHOH$), 6.66 (s, 1H, C_aH), 4.26 (br. d, $^3J_{HH}$ = 5.8, OH), 3.56 (dd, $^3J_{HH}$ = 7.9, 6.4, 1H, $CH(CO_2R)_2$), 2.50 (m, 1H, $CH_2CH(CO_2R)_2$), 1.72 (s, 9H, Boc $OC(CH_3)_3$), 1.47 (s, 9H, $OC(CH_3)_3$), 1.46 (s, 9H, $OC(CH_3)_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 169.2 ($RCO_2C(CH_3)_3$), 169.1 ($RCO_2C(CH_3)_3$), 151.7 ($NCO_2C(CH_3)_3$), 142.7 (C_h), 136.5 (C_g), 129.1 (C_b), 124.6 (C_d), 123.2 (C_e), 121.1 (C_c), 115.9 (C_f), 108.3 (C_a), 85.3 (Boc $OC(CH_3)_3$), 81.6 ($OC(CH_3)_3$), 81.6

(O*C*(CH$_3$)$_3$), 65.6 (*C*HOH), 51.3 (*C*H(CO$_2$R)$_2$), 33.8 (*C*H$_2$CH(CO$_2$R)$_2$), 28.4 (Boc OC(*C*H$_3$)$_3$), 28.1 (OC(*C*H$_3$)$_3$).

Enantiomeric ratio of 97:3 was determined using chiral SFC analysis (Whelk 01 column, 20% IPA/hexane – iso 50%, 4 mL/min, 125 bar): t_R = 10.8 [minor, (R)], 11.3 [major, (S)].



Area Percent	Area	Retention Time	Height
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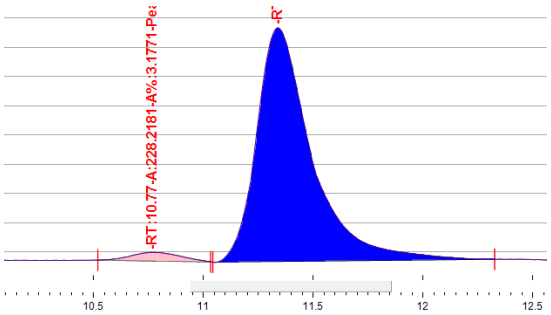
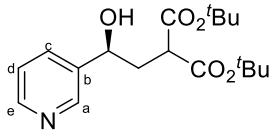
51.5523	18191.0848	10.44 min	964.5447



Area Percent	Area	Retention Time	Height
3.1771	228.2181	10.77 min	14.7381
96.8229	6955.0494	11.34 min	399.9636

Di-*tert*-butyl (*S*)-2-(2-hydroxy-2-(pyridin-3-yl)ethyl)malonate, 111i

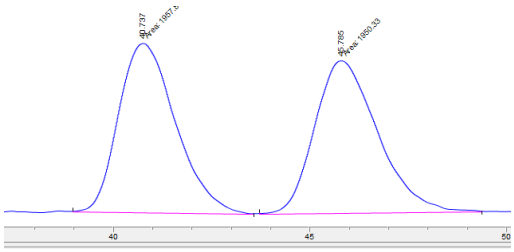


General procedure C, boronate formation condition iii), using (*R*)-**94** (50 mg, 0.14 mmol, 1.0 equiv), 3-bromopyridine (16 µL, 0.16 mmol, 1.2 equiv), *tert*-butyllithium (0.22 mL, 1.6 M solution in pentane, 2.4 equiv), MgBr$_2$·Et$_2$O (53 mg, 0.20 mmol, 1.5 equiv), oxidation was then performed using general procedure A to give **111i** as a colourless oil (29 mg, 63% yield).

R$_F$ 0.18 (50:50 petroleum ether/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 3196, 2978, 2934, 1723, 1477, 1393, 1368, 1250, 1161, 1138; **HRMS** (ESI): Calcd. for $C_{18}H_{27}NO_5Na^+$ *m*/*z* 360.1781, found *m*/*z* 360.1768 $[M+Na]^+$; $[\alpha]_D^{25}$ −20.4 (c = 1.30, 96:4 er);

^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.55 (br s., 1H, C$_a$*H*), 8.47 (br. d, $^3J_{HH}$ = 4.1, 1H, C$_e$*H*), 7.72 (dt, $^3J_{HH}$ = 7.9, $^4J_{HH}$ = 1.7, 1H C$_c$*H*), 7.26 (dd, $^3J_{HH}$ = 7.9, 4.8, 1H, C$_d$*H*), 4.81 (dd, $^3J_{HH}$ = 7.4, 5.6, 1H, C*H*OH), 3.50 (br, 1H, O*H*), 3.40 (t, $^3J_{HH}$ = 7.1, 1H, C*H*(CO$_2$R)$_2$), 2.26 – 2.18 (m, 2H, C*H*$_2$CH(CO$_2$R)$_2$), 1.45 (s, 9H, OC(C*H*$_3$)$_3$), 1.45 (s, 9H, OC(C*H*$_3$)$_3$); **^{13}C NMR** (CDCl$_3$, 101 MHz) δ 169.0 (R*C*O$_2$C(CH$_3$)$_3$), 168.9 (R*C*O$_2$C(CH$_3$)$_3$), 148.9 (*C$_e$*), 147.7 (*C$_a$*), 139.7 (*C$_b$*), 133.7 (*C$_c$*), 123.6 (*C$_d$*), 82.1 (O*C*(CH$_3$)$_3$), 82.1 (O*C*(CH$_3$)$_3$), 70.0 (*C*HOH), 51.2 (*C*H(CO$_2$R)$_2$), 37.9 (*C*H$_2$CH(CO$_2$R)$_2$), 28.1 (OC(*C*H$_3$)$_3$), 28.0 (OC(*C*H$_3$)$_3$).

Enantiomeric ratio of 96:4 was determined using chiral HPLC analysis (Chiralpak IA with guard, 3% IPA/hexane, 1 mL/min, 25 °C): t_R = 37.0 [major, (S)], 42.6 [minor, (R)].



Time	Type	Area	Height	Width	Area%
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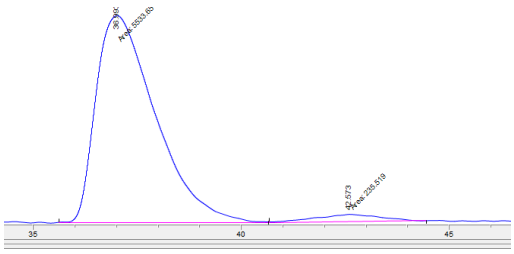
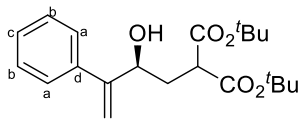
45.785	MM	1950.3	17.4	1.8714	49.904



Time	Type	Area	Height	Width	Area%
36.993	MM	5533.7	55.5	1.6627	95.918
42.573	MM	235.5	2.1	1.8966	4.082

Di-*tert*-butyl (*S*)-2-(2-hydroxy-3-phenylbut-3-en-1-yl)malonate, 111j



General procedure C, boronate formation condition ii), α-Styryllithium was synthesised according to procedure:

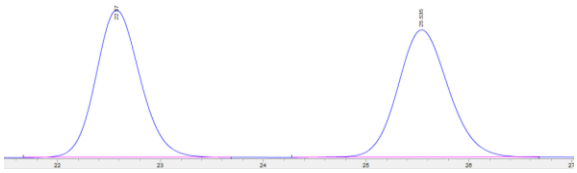
α-Bromostyrene (21 µL, 0.16 mmol, 1.2 equiv) was added to a flame dried Schlenk flask and dissolved in anhydrous THF (0.5 mL) then cooled to −78 °C. *tert*-Butyllithium (0.21 mL, 1.7 M solution in pentane, 2.5 equiv) was added dropwise and the reaction stirred at −78 °C for 1 hour.

Using (*R*)-**94** (50 mg, 0.14 mmol, 1.0 equiv), α-styryllithium (1.2 equiv), $MgBr_2 \cdot Et_2O$ (53 mg, 0.20 mmol, 1.5 equiv), a quantitative crude NMR yield was recorded of the product boronic ester (**110j**) before oxidation using general procedure A to yield **111j** as a white solid (22 mg, 45% yield).

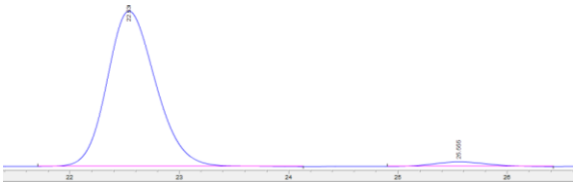
R_F 0.37 (80:20 petroleum ether/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 3443, 2977, 2932, 1721, 1456, 1368, 1251, 1141; **HRMS** (ESI): Calcd. for $C_{21}H_{30}O_5Na^+$ ($[M+Na]^+$) *m/z* 385.1985, found *m/z* 385.1993; $[\alpha]_D^{25}$ 20.8 (c = 0.86, 97:3 er);

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39 – 7.26 (m, 3H, C_aH, C_bH, C_cH), 5.42 (br. t, $^2J_{HH}$ = 1.3, $^4J_{HH}$ = 1.3, 1H, C=CH_2), 5.35 (br, 1H, C=CH_2), 4.72 (br. dt, $^3J_{HH}$ = 8.0, 3.4, 1H, C*H*OH), 3.45 (dd, $^3J_{HH}$ = 8.7, 5.5, 1H, C*H*($CO_2R)_2$), 2.40 (br. d, $^3J_{HH}$ = 4.6, 1H, O*H*), 2.17 (ddd, $^2J_{HH}$ = 14.4, $^3J_{HH}$ = 8.7, 3.4, 1H, CH_2CH($CO_2R)_2$), 1.95 (ddd, $^2J_{HH}$ = 14.5, $^3J_{HH}$ = 8.9, 5.5, 1H, CH_2CH($CO_2R)_2$), 1.45 (s, 9H, OC(C$H_3)_3$), 1.43 (s, 9H, OC(C$H_3)_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 169.4 (R*C*O_2C($CH_3)_3$), 169.2 (R*C*O_2C($CH_3)_3$), 151.3 (*C*=CH_2), 140.0 (C_d), 128.7 (C_b), 127.9 (C_c), 127.0 (C_a), 113.0 (C=*C*H_2), 81.9 (O*C*($CH_3)_3$), 81.7 (O*C*($CH_3)_3$), 71.5 (*C*HOH), 51.2 (*C*H($CO_2R)_2$), 35.0 (*C*H_2CH($CO_2R)_2$), 28.1 (OC(*C*$H_3)_3$), 28.0 (OC(*C*$H_3)_3$).

Enantiomeric ratio of 97:3 was determined using chiral HPLC analysis (Chiralpak IA with guard, 1% IPA/hexane, 1 mL/min, 25 °C): t_R = 22.5 [major, (S)], 25.6 [minor, (R)].

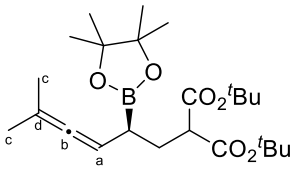


Time	Type	Area	Height	Width	Area%
22.571	BB	2648	88.1	0.4513	50.237
25.535	BB	2623	76.2	0.5183	49.763



Time	Type	Area	Height	Width	Area%
22.536	BB	5600	181.1	0.4718	96.818
25.555	BB	184.1	5.3	0.4099	3.182

Di-*tert*-butyl (*S*)-2-(5-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexa-3,4-dien-1-yl)malonate, 110k



General procedure C, boronate formation condition ii), (3-methylbuta-1,2-dien-1-yl)lithium was synthesised according to the following literature procedure:[162]

3-Methylbuta-1,2-diene (16 µL, 0.16 mmol, 1.2 equiv) was added to a flame dried Schlenk flask and dissolved in anhydrous THF (0.5 mL) then cooled to −78 °C. *tert*-Butyllithium (1.7 M solution in pentane, 1.2 equiv) was added dropwise and the reaction stirred at −78 °C for 30 minutes and then warmed to room temperature and stirred for 5 minutes.

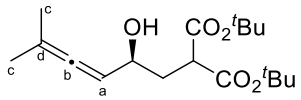
Using (*R*)-**94** (50 mg, 0.14 mmol, 1.0 equiv), (3-methylbuta-1,2-dien-1-yl)lithium (1.2 equiv), $MgBr_2{\cdot}Et_2O$ (53 mg, 0.20 mmol, 1.5 equiv), to yield **110k** as a colourless oil (45 mg, 76% yield).

R_F 0.41 (90:10 petroleum ether/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 2977, 2932, 1743, 1726, 1478, 1455, 1367, 1323, 1257, 1140; **HRMS** (ESI): Calcd. for $C_{24}H_{41}BO_6Na^+$ ($[M+Na]^+$) *m*/*z* 459.2888, found *m*/*z* 459.2877; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ −5.5 (c = 2.00, 97:3 er);

^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.94 (dsept, $^3J_{HH}$ = 7.7, $^5J_{HH}$ = 2.8, 1H, C_aH), 3.34 (dd, $^3J_{HH}$ = 8.6, 6.5, 1H, $CH(CO_2R)_2$), 2.04 (ddd, $^2J_{HH}$ = 13.8, $^3J_{HH}$ = 8.6, 6.5, 1H, $CH_2CH(CO_2R)_2$), 1.87 (ddd, $^2J_{HH}$ = 13.8, $^3J_{HH}$ = 9.5, 6.5, 1H, $CH_2CH(CO_2R)_2$), 1.66 (d, $^5J_{HH}$ = 2.8, 6H, C_cH), 1.63 (ddd, $^3J_{HH}$ = 9.5, 7.7, 6.5, 1H, CH(Bpin)), 1.44 (s, 9H, $OC(CH_3)_3$), 1.44 (s, 9H, $OC(CH_3)_3$), 1.23 (s, 12H, pinacol CH_3); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 201.9 (C_b), 169.3 ($RCO_2C(CH_3)_3$), 168.8 ($RCO_2C(CH_3)_3$), 95.9 (C_d), 88.5 (C_a), 83.2 (pinacol $OC(R)(CH_3)_2$), 81.0 ($OC(CH_3)_3$), 81.0 ($OC(CH_3)_3$), 52.7 ($CH(CO_2R)_2$), 29.1 ($CH_2CH(CO_2R)_2$), 28.0 ($OC(CH_3)_3$), 27.9

(OC(*C*H$_3$)$_3$), 24.7 (*C$_c$*), 24.6 (*C$_c$*), 22.5 (*C*H(Bpin)), 20.8 (pinacol *C*H$_3$), 20.7 (pinacol *C*H$_3$); **^{11}B NMR** (CDCl$_3$, 128 MHz) δ 31.7.

Di-*tert*-butyl (*S*)-2-(2-hydroxy-5-methylhexa-3,4-dien-1-yl)malonate, 111k

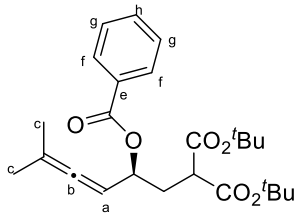


Oxidation of **110k** performed using general procedure A to give **111k** as a colourless oil.

R$_F$ 0.35 (80:20 petroleum ether/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 3444, 2978, 2934, 1725, 1455, 1393, 1368, 1254, 1140; **HRMS** (ESI): Calcd. for $C_{18}H_{30}O_5Na^+$ ([M+Na]$^+$) *m*/*z* 359.1985, found *m*/*z* 349.1996; $[\alpha]_D^{25}$ −4.7 (c = 1.23, 97:3 er);

^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.45 (s, 9H, OC(C*H$_3$*)$_3$), 1.46 (s, 9H, OC(C*H$_3$*)$_3$), 1.71 (d, $^5J_{HH}$ = 2.1, 3H, C$_c$*H*), 1.72 (d, $^5J_{HH}$ = 2.8, 3H, C$_c$*H*), 1.88 (br. d, $^3J_{HH}$ = 5.1, 1H, O*H*), 2.00 (ddd, $^2J_{HH}$ = 14.2, $^3J_{HH}$ = 8.0, 6.5, 1H, C*H$_2$*CH(CO$_2$R)$_2$), 2.10 (ddd, $^2J_{HH}$ = 14.2, $^3J_{HH}$ = 7.7, 4.8, 1H, C*H$_2$*CH(CO$_2$R)$_2$), 3.40 (dd, $^3J_{HH}$ = 7.7, 6.5, 1H, C*H*(CO$_2$R)$_2$), 4.15 (br. ddt, $^3J_{HH}$ = 8.0, 5.0, 3.1, 1H, C*H*OH), 5.08 (nonet, $^3J_{HH}$, $^5J_{HH}$ = 2.9, 1H, C$_a$*H*); **^{13}C NMR** (CDCl$_3$, 101 MHz) δ 20.7 (*C$_c$*), 20.7 (*C$_c$*), 28.1 (OC(*C*H$_3$)$_3$), 28.1 (OC(*C*H$_3$)$_3$), 36.3 (*C*H$_2$CH(CO$_2$R)$_2$), 50.9 (*C*H(CO$_2$R)$_2$), 68.2 (*C*HOH), 81.6 (O*C*(CH$_3$)$_3$), 81.6 (O*C*(CH$_3$)$_3$), 93.33 (*C$_a$*), 99.5 (*C$_d$*), 169.2 (R*C*O$_2$C(CH$_3$)$_3$), 169.2 (R*C*O$_2$C(CH$_3$)$_3$), 199.9 (*C$_b$*).

Di-*tert*-butyl (*S*)-2-(2-(benzoyloxy)-5-methylhexa-3,4-dien-1-yl)malonate, 111k'



Esterification of **111k** performed using general procedure B to give **111k'** as a colourless oil (87% yield).

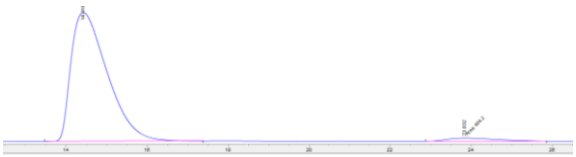
R$_F$ 0.46 (90:10 petroleum ether/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 2979, 2935, 2909, 1720, 1451, 1368, 1266, 1138; **HRMS** (ESI): Calcd. for $C_{25}H_{34}O_6Na^+$ ([M+Na]$^+$) *m*/*z* 453.2248, found *m*/*z* 453.2241; $[\alpha]_D^{25}$ −24.9 (c = 1.40, 97:3 er);

^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.03 (m, 2H, C$_f$*H*), 7.54 (tt, $^3J_{HH}$ = 7.4, $^4J_{HH}$ = 1.3, 1H, C$_h$*H*), 7.42 (m, 2H, C$_g$*H*), 5.47 (dt, $^3J_{HH}$ = 7.2, 6.0, 1H, C*H*(OBz)), 5.12 (nonet, $^3J_{HH}$, $^5J_{HH}$ = 2.8, 1H, C$_a$*H*) 3.37 (t, $^3J_{HH}$ = 7.3, 1H, C*H*(CO$_2$R)$_2$), 2.32 (m, 2H, C*H$_2$*CH(CO$_2$R)$_2$), 2.00 (ddd, $^2J_{HH}$ = 14.2, $^3J_{HH}$ = 8.0, 6.5, 1H, C*H$_2$*CH(CO$_2$R)$_2$), 1.88 (br. d, $^3J_{HH}$ = 5.1, 1H, O*H*), 1.68 (d, $^5J_{HH}$ = 2.9, 3H, C$_c$*H*), 1.64 (d, $^5J_{HH}$ = 2.8, 3H, C$_c$*H*), 1.44 (s, 9H, OC(C*H$_3$*)$_3$), 1.43 (s, 9H, OC(C*H$_3$*)$_3$); **^{13}C NMR** (CDCl$_3$, 101 MHz) δ 202.0 (*C$_b$*), 168.4 (R*C*O$_2$C(CH$_3$)$_3$), 168.4 (R*C*O$_2$C(CH$_3$)$_3$), 165.6 (Ph*C*O$_2$R), 132.8 (*C$_h$*H), 130.6 (*C$_e$*H), 129.6 (*C$_f$*H), 128.2 (*C$_g$*H), 98.8 (*C$_d$*), 88.8 (*C$_a$*),20.2

(C_c), 81.7 (O*C*(CH_3)$_3$), 81.7 (O*C*(CH_3)$_3$), 71.0 (*C*H(OBz)), 50.6 (*C*H(CO_2R)$_2$), 33.0 (*C*H_2CH(CO_2R)$_2$), 27.9 (OC(*C*H_3)$_3$), 27.9 (OC(*C*H_3)$_3$), 20.2 (C_c).

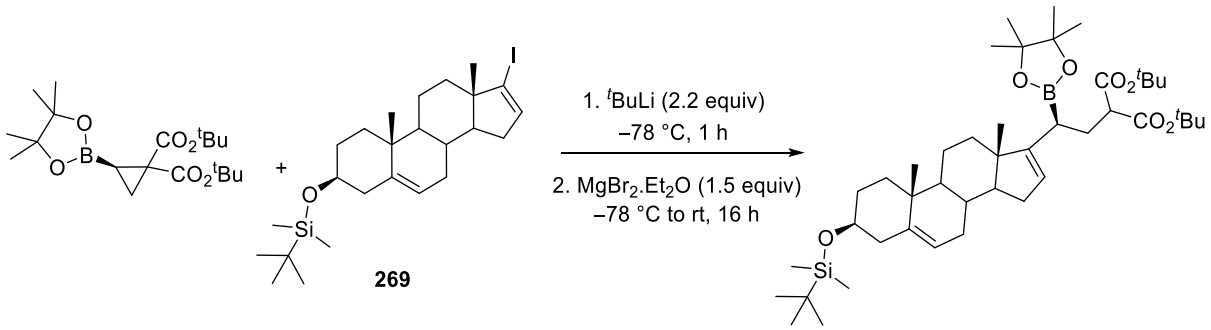
Enantiomeric ratio of 97:3 was determined using chiral HPLC analysis (Chiralpak IC with guard, 0.5% IPA/hexane, 1 mL/min, 25 °C): t_R = 14.4 [major, (S)], 23.8 [minor, (R)].

Time	Type	Area	Height	Width	Area%
14.935	MM	1819.3	30.2	1.0026	50.017
24.205	MM	1818	18.9	1.6069	49.983



Time	Type	Area	Height	Width	Area%
14.418	BB	12932.8	208.1	0.9032	96.535
23.832	MM	464.2	5.4	1.4403	3.465

Di-*tert*-butyl 2-((2*S*)-2-((3*S*,10*R*,13*S*)-3-((*tert*-butyldimethylsilyl)oxy)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)malonate, 110l



General procedure C, boronate formation condition iii), using (*R*)-**94** (50 mg, 0.14 mmol, 1.0 equiv), vinyl iodide **269** (77 mg, 0.15 mmol, 1.1 equiv), *tert*-butyllithium (0.19 mL, 1.6 M solution in pentane, 2.2 equiv), $MgBr_2 \cdot Et_2O$ (53 mg, 0.20 mmol, 1.5 equiv), to yield **110l** as a colourless oil (67 mg, 65% yield).

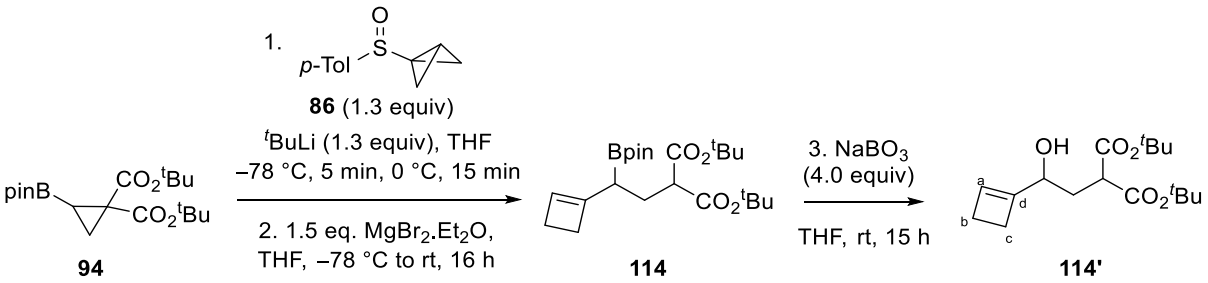
Notes: (A) vinyl iodide **269** was prepared by previous researcher following a literature procedure.[163]

R_F 0.50 (90:10 petroleum ether/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 2975, 2931, 2854, 1744, 1727, 1462, 1368, 1322, 1251, 1140; **HRMS** (ESI): Calcd. for $C_{44}H_{75}BO_7SiNa^+$ ([M+Na]$^+$) *m*/*z* 777.5267, found *m*/*z* 777.5298; $[\alpha]_D^{25}$ −32.0 (c = 3.04);

^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.41 (br., 1H, alkene C*H*), 5.32 (br., 1H, alkene C*H*), 3.48 (tt, $^3J_{HH}$ = 10.9, 4.8, 1H, C*H*OSi(CH_2)$_2$R), 3.23 (t, $^3J_{HH}$ = 7.7, 7.1, 1H, C*H*(CO_2R)$_2$), 2.29 – 2.14 (m, 2H, CH_2), 2.09 – 1.47 (m, 14H, 6 × CH_2, C*H*, C*H*(Bpin)), 1.44 (s, 9H, OC(CH_3)$_3$), 1.44 (s,

9H, OC(CH_3)$_3$), 1.35 – 1.24 (m, 2H, CH, CH_2), 1.21 (s, 6H, pinacol CH_3), 1.20 (s, 6H, pinacol CH_3), 1.02 (s, 3H, CH_3), 1.07 – 0.98 (m, 2H, CH, CH_2), 0.88 (s, 9H, Si(C(CH_3)$_3$), 0.77 (s, 3H, CH_3), 0.05 (s, 6H, Si(CH_3)$_2$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 169.4 (R*C*O$_2$C(CH$_3$)$_3$), 169.0 (R*C*O$_2$C(CH$_3$)$_3$), 155.3 (alkene *C*), 142.0 (alkene *C*), 123.2 (alkene *C*H), 121.2 (alkene *C*H), 83.3 (pinacol O*C*(R)(CH$_3$)$_2$), 81.2 (O*C*(CH$_3$)$_3$), 81.1 (O*C*(CH$_3$)$_3$), 72.8 (*C*HOSi(CH$_2$)$_2$R)), 57.1 (*C*H), 53.3 (*C*H(CO$_2$R)$_2$), 51.0 (*C*H), 47.2 (*C*), 43.0 (*C*H$_2$), 37.5 (*C*H$_2$), 37.0 (*C*), 34.5 (*C*H$_2$), 32.3 (*C*H$_2$), 31.8 (*C*H$_2$), 31.5 (*C*H$_2$), 30.8 (*C*H), 30.5 (*C*H$_2$), 26.1 (Si(C(*C*H$_3$)$_3$), 24.9 (pinacol *C*H$_3$), 24.8 (pinacol *C*H$_3$), 20.9 (*C*H$_2$), 20.6 (br, *C*H(Bpin)), 19.5 (*C*H$_3$), 18.4 (Si(*C*(CH$_3$)$_3$), 16.37 (*C*H$_3$), −4.4 (Si(*C*H$_3$)$_2$); **^{11}B NMR** ($CDCl_3$, 128 MHz) δ 32.4.

Di-*tert*-butyl 2-(2-(cyclobut-1-en-1-yl)-2-hydroxyethyl)malonate, 114'



(±)**-94** (50 mg, 0.14 mmol, 1.0 equiv) and sulfoxide **86**[A] (34 mg, 0.18 mmol, 1.3 equiv) were added to a flame dried Schlenk tube, evacuated and purged with nitrogen then dissolved in anhydrous THF (1.3 mL). At –78 °C, *tert*-butyllithium (1.7 M solution in pentane, 1.3 equiv) was added dropwise and the reaction stirred at –78 °C for 5 minutes. The reaction was then warmed to room temperature and stirred for 15 minutes. At –78 °C, $MgBr_2.Et_2O$ (53 mg, 0.20 mmol, 1.5 equiv) was added and the reaction was left to warm slowly to room temperature overnight. After this time, water (10 mL) and diethyl ether (10 mL) were added and the phases separated. The aqueous phase was extracted with diethyl ether (3 × 10 mL) and the combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crude reaction mixture was added to a pre-equilibrated column (98:2 pentane/ethyl acetate, 10 g Biotage ZIP® cartridge) with petroleum ether (3 × 0.5 mL) and eluted within 10 minutes of contact with silica (98:2 → 80:20 pentane/ethyl acetate).

Boronic ester **114** coeluted with an unknown side product so the mixture was oxidised. In a round bottom flask, the mixture (28 mg) was dissolved in THF (0.5 mL) and $NaBO_3 \cdot 4H_2O$ (90 mg, 0.59 mmol, 4.0 equiv) was added at room temperature. The reaction was stirred at room temperature overnight. Water (5 mL) and ethyl acetate (5 mL) were added and the phases

separated. The aqueous phase was extracted with ethyl acetate (3 × 10 mL) and the combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (100:0 → 70:30 hexane/ethyl acetate) to give **65h** as a colourless oil (9.0 mg, 0.029 mmol, 21% yield).

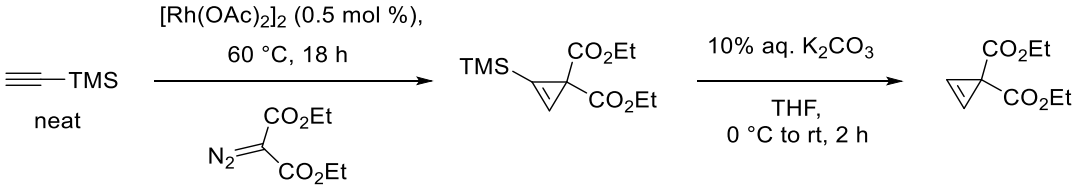
Notes: (A) sulfoxide **86** was prepared following a literature procedure.[80]

R_F 0.34 (80:20 petroleum ether/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 3449, 2977, 2925, 1724, 1456, 1393, 1368, 1255; **HRMS** (ESI): Calcd. for $C_{17}H_{28}O_5Na^+$ ($[M+Na]^+$) *m*/*z* 335.1829, found *m*/*z* 335.1828;

^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.90 (s, 1H, C_aH), 4.13 (m, 1H, C*H*(OH)), 3.40 (dd, $^3J_{HH}$ = 7.9, 6.2, 1H, C*H*($CO_2R)_2$), 2.49 (m, 2H, C_cH_2), 2.36 (m, 2H, C_bH_2), 2.15 (ddd, $^2J_{HH}$ = 14.4, $^3J_{HH}$ = 7.9, 4.0, 1H, CH_2CH($CO_2R)_2$), 1.98 (ddd, $^2J_{HH}$ = 14.4, $^3J_{HH}$ = 8.6, 6.2, 1H, CH_2CH($CO_2R)_2$), 1.45 (s, 9H, OC(C$H_3)_3$), 1.45 (s, 9H, OC(C$H_3)_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 169.3 (R*C*O_2C($CH_3)_3$), 169.2 (R*C*O_2C($CH_3)_3$), 150.5 (C_d), 128.7 (C_a), 81.8 (O*C*($CH_3)_3$), 81.7 (O*C*($CH_3)_3$), 68.3 (*C*H(OH)), 50.9 (*C*H($CO_2R)_2$), 34.0 (*C*H_2CH($CO_2R)_2$), 28.8 (C_c), 28.1 (OC(*C*$H_3)_3$), 28.1 (OC(*C*$H_3)_3$), 26.5 (C_b).

6.2.7. Analysis of the necessity for *tert*-butyl esters

Diethyl cycloprop-2-ene-1,1-dicarboxylate



Following a modified literature procedure:[86]

A round bottom flask fitted with a condenser and charged with $Rh_2(OAc)_4$ (0.010 g, 0.022 mmol, 0.5 mol%) was evacuated and purged with nitrogen. Trimethylsilyl acetylene (11 mL) was added and the solution was heated to reflux. A solution of diethyl 2-diazomalonate[A] (0.83 g, 4.5 mmol) in trimethylsilyl acetylene (0.7 mL) was added to the reaction flask *via* syringe pump over 16 hours. After complete addition, reflux was maintained for a further 5 hours. The reaction mixture was then filtered through a pad of silica and the solvent was then removed *in vacuo*. The crude mixture was then dissolved in THF (23 mL). A solution of 10% aq. K_2CO_3 (8.5 mL) was added dropwise at 0 °C and the mixture was stirred

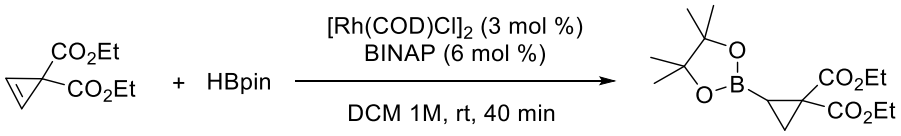
at room temperature for 1 hour. The phases were separated, and the organic phase was concentrated under reduced pressure. The phases were recombined with the addition of water (20 mL) and diethyl ether (20 mL) and the aqueous phase was extracted with diethyl ether (3 × 20 mL). Combined organic phases were washed with brine, dried dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (100:0 → 70:30 pentane/ethyl acetate) to give diethyl cycloprop-2-ene-1,1-dicarboxylate as a brown oil (0.56 g, 68% yield).

Notes: (A) diethyl 2-diazomalonate was prepared following a literature procedure.[160]

R_F 0.28 (75:25 petroleum ether/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 3168, 3118, 2982, 2942, 1725, 1447, 1367, 1278; **HRMS** (ESI): Calcd. for $C_9H_{13}O_4^+$ ($[M+H]^+$) *m*/*z* 185.0808, found *m*/*z* 185.0804;

^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.91 (s, 2H, *H*C(R)=C(R)*H*), 4.18 (q, $^3J_{HH}$ = 7.1, 4H, OCC*H*$_2$CH$_3$), 1.26 (t, $^3J_{HH}$ = 7.1, 6H, OCCH$_2$C*H*$_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 171.2 (R*C*O$_2$C(CH$_3$)$_3$), 102.8 (H*C*(R)=*C*(R)H), 61.4 (OCC*H*$_2$CH$_3$), 30.4 (*C*(CO$_2$R)$_2$), 14.3 (OCCH$_2$*C*H$_3$).

Diethyl 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropane-1,1-dicarboxylate, 115



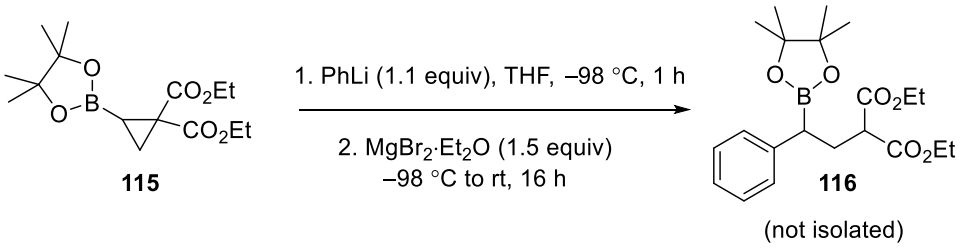
Following a modified literature procedure:[86]

A flame dried Schlenk flask was charged with $[Rh(COD)Cl]_2$ (29 mg, 0.058 mmol, 0.030 equiv) and (±)-BINAP (72 mg, 0.12 mmol, 0.06 eq), evacuated and purged with nitrogen. Anhydrous DCM (1.9 mL) was added and the reaction was stirred for 3 minutes at room temperature. HBpin (0.34 mL, 2.3 mmol, 1.2 eq) and diethyl cycloprop-2-ene-1,1-dicarboxylate (349 mg, 1.89 mmol) were added successively. The mixture was stirred at room temperature for 40 minutes before filtration through a pad of silica. The crude mixture was concentrated under reduced pressure and added to a pre-equilibrated column and eluted within 15 minutes of contact with silica (98:2 → 60:40 pentane/ethyl acetate) to yield **115** as a yellow oil (0.370 g, 63% yield).

R_F 0.5 (75:25 petroleum ether/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 2979, 2951, 1732, 1436, 1413, 1335, 1288, 1233, 1141; **HRMS** (ESI): Calcd. for $C_{15}H_{26}O_6B^+$ ($[M+H]^+$) *m*/*z* 313.1817, found *m*/*z* 313.1815;

^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.28 – 4.09 (m, 4H, OCC*H*$_2$CH$_3$), 1.50 (app. d, $^3J_{HH}$ = 9.5, 2H, C*H*$_2$(R)(R')), 1.29 (t, $^3J_{HH}$ = 7.2, 3H, OCCH$_2$C*H*$_3$), 1.24 (t, $^3J_{HH}$ = 7.3, 3H, OCCH$_2$C*H*$_3$), 1.23 (s, 6H, pinacol C*H*$_3$), 1.22 (s, 6H, pinacol C*H*$_3$), 1.08 (dd, $^3J_{HH}$ = 10.1, 8.9, 1H, pinB-C*H*(R)(R')); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 170.5 (R*C*O$_2$Et), 168.9 (R*C*O$_2$Et), 83.9 (pinacol O*C*(R)(CH$_3$)$_2$), 61.7 (O*C*H$_2$CH$_3$), 61.5 (O*C*H$_2$CH$_3$), 34.2 (*C*(R)(R')(CO$_2$Et)$_2$), 24.9 (pinacol *C*H$_3$), 24.9 (pinacol *C*H$_3$), 18.8 (*C*H$_2$(R)(R')), 14.1 (OCH$_2$*C*H$_3$), 11.6 (br., *C*HBpin); **^{11}B NMR** ($CDCl_3$, 128 MHz) δ 29.1.

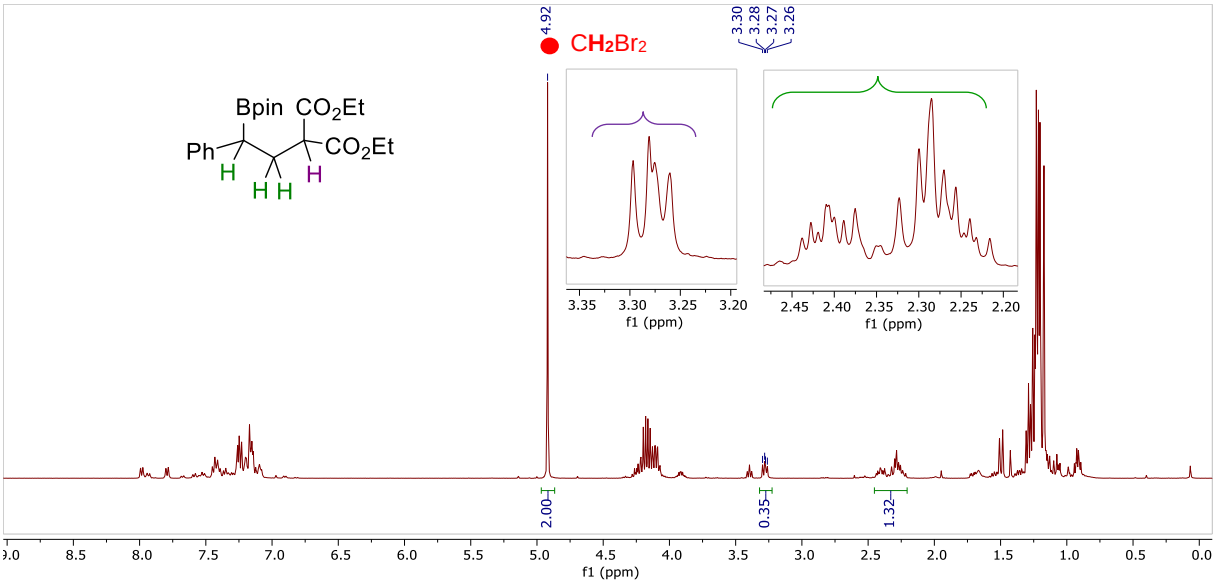
Two component reaction employing diethyl ester 115



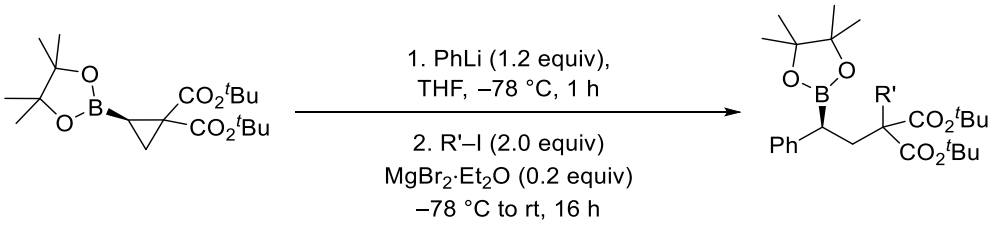
A flame dried Schlenk flask was charged with **115** (42 mg, 0.14 mmol), evacuated and purged with nitrogen before the addition of anhydrous THF (1 mL). The reaction flask was cooled to at −98 °C (methanol/liquid nitrogen) before the dropwise addition of phenyllithium (0.08 mL, 1.9 M solution in dibutylether, 1.1 equiv). The reaction was then stirred at −98 °C for 1 hour before $MgBr_2.Et_2O$ (52 mg, 0.20 mmol, 1.5 equiv) was added as a solid under a positive flow of nitrogen at −98 °C and the reaction stirred overnight whilst warming slowly to room temperature. Water (10 mL) and diethyl ether (10 mL) were added and the phases separated. The aqueous phase was extracted with diethyl ether (3 × 10 mL) and the combined organic phases were washed with brine, dried ($MgSO_4$), filtered and concentrated. A quantitative ^{1}H NMR spectrum of the crude reaction in the presence of CH_2Br_2 (1.0 eq) as an internal standard showed the ring opened product **116** (35% NMR yield).

HRMS (ESI): Calcd. for $C_{21}H_{32}BO_6^+$ ($[M+H]^+$) *m*/*z* 391.2286, found *m*/*z* 391.2285

Crude ^{1}H NMR ($CDCl_3$, 400 MHz):



6.2.8. General procedure D for the boronate formation and subsequent 1,2-metallate rearrangement/ring opening then electrophilic trapping of (*R*)-94

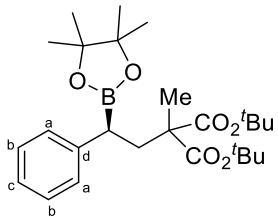


A flame dried Schlenk flask was charged with (*R*)-**94** (50 mg, 0.14 mmol, 1.0 equiv), evacuated and purged with nitrogen before the addition of anhydrous THF (1 mL). The reaction flask was cooled to −78 °C before the dropwise addition of phenyllithium (0.09 mL, 1.9 M solution in dibutylether, 1.2 equiv). The reaction was stirred at −78 °C for 1 hour. $MgBr_2.Et_2O$ (7.0 mg, 0.027 mmol, 0.2 equiv) was weighed into a vial in a nitrogen atmosphere glovebox and the vial sealed with a septum before the addition of diethyl ether, (0.2 mL) to the vial. Sequentially, the electrophile (2 equiv) and the solution of $MgBr_2.Et_2O$ were added dropwise to the flask containing the boronate complex at −78 °C. The reaction was stirred overnight whilst warming slowly to room temperature. Water (10 mL) and diethyl ether (10 mL) were added and the phases separated. The aqueous phase was extracted with diethyl ether (3 × 10 mL) and the combined organic phases were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. A quantitative ^1H NMR spectrum of the crude reaction mixture was recorded to determine the NMR yield. The crude reaction mixture was then added to a pre-equilibrated column (98:2 pentane/ethyl acetate, 10 g Biotage ZIP cartridge) with petroleum

ether (2 × 0.5 mL) and eluted within 10 minutes of contact with silica (98:2 → 80:20 pentane/ethyl acetate) to limit the protodeboronation of product boronic esters.

6.2.9. Reaction scope for the three-component reaction

Di-*tert*-butyl (*S*)-2-methyl-2-(2-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)malonate, 117a

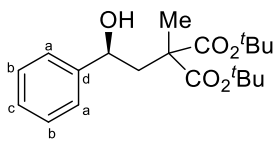


General procedure D using (*R*)-**94** (50 mg, 0.14 mmol, 1.0 equiv), phenyllithium (0.09 mL, 1.9 M solution in dibutyl ether, 1.2 equiv), methyl iodide (17 µL, 0.28 mmol, 2.0 equiv), $MgBr_2 \cdot Et_2O$ (7.0 mg, 0.028 mmol, 0.2 equiv), to yield **117a** as a colourless oil (48 mg, 77% yield).

R_F 0.42 (90:10 petroleum ether/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 2977, 2933, 1725, 1453, 1368, 1324, 1253, 1141; **HRMS** (ESI): Calcd. for $C_{26}H_{41}BO_6Na^+$ ($[M+Na]^+$) *m*/*z* 483.2888, found *m*/*z* 483.2904; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ 8.4 (*c* = 1.67, 97:3 er);

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.21 – 7.18 (m, 4H, C_aH, C_bH), 7.10 (m, 1H, C_cH), 2.51 (dd, $^2J_{HH}$ = 15.0, $^3J_{HH}$ = 9.7, 1H, $CH_2C(Me)(CO_2R)_2$), 2.22 (dd, $^3J_{HH}$ = 9.7, 4.5, 1H, $CH(Ph)(Bpin)$), 2.21 (dd, $^2J_{HH}$ = 15.0, $^3J_{HH}$ = 4.5, 1H, $CH_2C(Me)(CO_2R)_2$), 1.43 (s, 9H, $OC(CH_3)_3$), 1.37 (s, 9H, $OC(CH_3)_3$), 1.28 (s, 3H, CH_3), 1.14 (s, 6H, pinacol CH_3), 1.12 (s, 6H, pinacol CH_3); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 172.0 ($RCO_2C(CH_3)_3$), 171.5 ($RCO_2C(CH_3)_3$), 143.8 (C_d), 128.4 (C_b, C_a), 125.3 (C_c), 83.5 (pinacol $OC(R)(CH_3)_2$), 81.0 ($OC(CH_3)_3$), 80.9 ($OC(CH_3)_3$), 55.7 ($C(Me)(CO_2R)_2$), 37.5 ($CH_2C(Me)(CO_2R)_2$), 28.0 ($OC(CH_3)_3$), 28.0 ($OC(CH_3)_3$), 24.7 (pinacol CH_3), 24.6 (pinacol CH_3), 20.0 (CH_3); **^{11}B NMR** ($CDCl_3$, 128 MHz) δ 31.9.

Di-*tert*-butyl (*S*)-2-(2-hydroxy-2-phenylethyl)-2-methylmalonate, 117a'



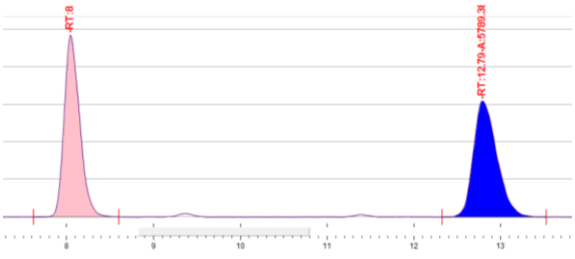
Oxidation of **117a** performed using general procedure A to give **117a'** as a white solid.

R_F 0.47 (80:20 petroleum ether/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 3445, 2979, 2935, 1722, 1455, 1394, 1368, 1283, 1249, 1154, 1116; **HRMS** (ESI): Calcd. for $C_{20}H_{30}O_5Na^+$ ($[M+Na]^+$) *m*/*z* 373.1985, found *m*/*z* 373.1999; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ −20.7 (*c* = 1.21, 97:3 er);

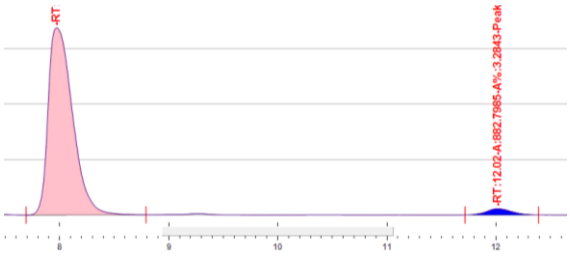
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39 – 7.32 (m, 4H, C_aH, C_bH), 7.25 (tt, $^3J_{HH}$ = 7.0, $^4J_{HH}$ = 1.6, 1H, C_cH), 4.85 (br. dt, $^3J_{HH}$ = 10.3, 2.8, 1H, $CHOH$), 3.34 (br. d, $^3J_{HH}$ = 3.9, 1H, OH), 2.38 (dd, $^2J_{HH}$ = 15.0, $^3J_{HH}$ = 10.3, 1H, $CH_2C(Me)(CO_2R)_2$), 1.99 (dd, $^2J_{HH}$ = 15.0, $^3J_{HH}$ = 2.3, 1H,

C*H*$_2$C(Me)(CO$_2$R)$_2$), 1.51 (s, 3H, C*H*$_3$), 1.50 (s, 9H, OC(C*H*$_3$)$_3$), 1.45 (s, 9H, OC(C*H*$_3$)$_3$); **^{13}C NMR** (CDCl$_3$, 101 MHz) δ 172.8 (R*C*O$_2$C(CH$_3$)$_3$), 172.1 (R*C*O$_2$C(CH$_3$)$_3$), 145.5 (*C*$_d$), 128.5 (*C*$_b$), 127.4 (*C*$_c$), 125.7 (*C*$_a$), 82.0 (O*C*(CH$_3$)$_3$), 81.8 (O*C*(CH$_3$)$_3$), 70.9 (*C*HOH), 54.5 (*C*(Me)(CO$_2$R)$_2$), 45.3 (*C*H$_2$C(Me)(CO$_2$R)$_2$), 28.0 (OC(*C*H$_3$)$_3$), 28.0 (OC(*C*H$_3$)$_3$), 20.4 (*C*H$_3$).

Enantiomeric ratio of 97:3 was determined using chiral SFC analysis (Whelk 01 column, 10% IPA/hexane – iso 10%, 4 mL/min, 125 bar): t_R = 8.0 [major, (S)], 12.0 [minor, (R)].

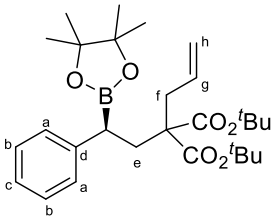


Area Percent	Area	Retention Time	Height
50.7846	5973.9722	8.04 min	484.415
49.2154	5789.3817	12.79 min	309.2437



Area Percent	Area	Retention Time	Height
96.7157	25996.8294	7.97 min	1685.1888
3.2843	882.7985	12.02 min	55.5427

Di-*tert*-butyl (*S*)-2-allyl-2-(2-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)malonate, 117b

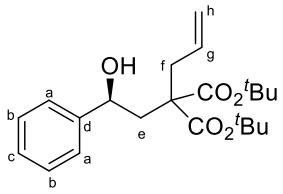


General procedure D using (*R*)-**94** (50 mg, 0.14 mmol, 1.0 equiv), phenyllithium (0.09 mL, 1.9 M solution in dibutyl ether, 1.2 equiv), allyl iodide (25 µL, 0.27 mmol, 2.0 equiv), MgBr$_2$·Et$_2$O (7.0 mg, 0.028 mmol, 0.2 equiv), to yield **117b** as a colourless oil (58 mg, 88% yield).

R$_F$ 0.44 (90:10 petroleum ether/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 3079, 2977, 2933, 1723, 1640, 1600, 1478, 1453, 1367, 1324, 1251, 1140; **HRMS** (ESI): Calcd. for C$_{26}$H$_{43}$BO$_6$Na$^+$ ([M+Na]$^+$) *m*/*z* 509.3045, found *m*/*z* 509.3042; **$[\alpha]_D^{25}$** 18.4 (*c* = 2.65, 97:3 er);

^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.21 – 7.18 (m, 4H, C$_a$*H*, C$_b$*H*), 7.09 (m, 1H, C$_c$*H*), 5.67 (dddd, $^3J_{HH}$ = 17.1, 10.2, 7.7, 6.9, 1H, C$_g$*H*), 4.91 (m, 1H, C$_h$*H*$_2$), 4.96 (m, 1H, C$_h$*H*$_2$), 2.57 (dd, $^2J_{HH}$ = 16.3, $^3J_{HH}$ = 8.4, 1H, C$_e$*H*$_2$), 2.43-2.53 (m, 2H, C$_f$*H*$_2$), 2.23 – 2.18 (m, 2H, C*H*(Ph)(Bpin), C$_e$*H*$_2$,), 1.43 (s, 9H, OC(C*H*$_3$)$_3$), 1.32 (s, 9H, OC(C*H*$_3$)$_3$), 1.13 (s, 6H, pinacol C*H*$_3$), 1.12 (s, 6H, pinacol C*H*$_3$); **^{13}C NMR** (CDCl$_3$, 101 MHz) δ 170.6 (R*C*O$_2$C(CH$_3$)$_3$), 170.5 (R*C*O$_2$C(CH$_3$)$_3$), 143.6 (*C*$_d$), 133.4 (*C*$_h$), 128.7 (*C*$_a$), 128.4 (*C*$_b$), 125.4 (*C*$_c$), 118.3 (*C*$_h$), 83.5 (pinacol O*C*(R)(CH$_3$)$_2$), 81.2 (O*C*(CH$_3$)$_3$), 81.1 (O*C*(CH$_3$)$_3$), 59.3 (*C*(CO$_2$R)$_2$), 36.9 (*C*$_f$), 34.1 (*C*$_e$), 28.1 (OC(*C*H$_3$)$_3$), 28.0 (OC(*C*H$_3$)$_3$), 24.8 (pinacol *C*H$_3$), 24.5 (pinacol *C*H$_3$); **^{11}B NMR** (CDCl$_3$, 128 MHz) δ 32.1.

Di-*tert*-butyl (*S*)-2-allyl-2-(2-hydroxy-2-phenylethyl)malonate, 117b'

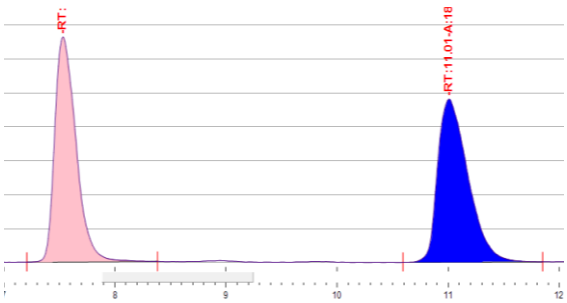


Oxidation of **117b** performed using general procedure A to give **117b'** as a white solid.

R_F 0.43 (80:20 petroleum ether/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 3364, 3078, 2977, 2932, 1716 (C=O), 1640 (C=C), 1565, 1455, 1393, 1368, 1295, 1248, 1223, 1144; **HRMS** (ESI): Calcd. for $C_{22}H_{32}O_5Na^+$ ($[M+Na]^+$) *m/z* 399.2142, found *m/z* 399.2150; $[\alpha]_D^{25}$ −5.1 (*c* = 1.65, 97:3 er);

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37 – 7.31 (m, 4H, C_aH, C_bH), 7.25 (tt, $^3J_{HH}$ = 6.7, $^4J_{HH}$ = 1.9, 1H, C_cH), 5.71 (dddd, $^3J_{HH}$ = 16.9, 10.1, 7.9, 6.7, 1H, C_gH), 5.19 – 5.10 (m, 2H, C_hH_2), 4.86 (ddd, $^3J_{HH}$ = 10.3, 3.4, 2.2, 1H, CHO*H*), 2.87 (br. d, $^3J_{HH}$ = 3.4, 1H, O*H*), 2.85 (ddt, $^2J_{HH}$ = 14.4, $^3J_{HH}$ = 6.7, $^4J_{HH}$ = 1.2, 1H, C_fH_2), 2.69 (ddt, $^2J_{HH}$ = 14.4, $^3J_{HH}$ = 7.9, $^4J_{HH}$ = 0.9, 1H, C_fH_2), 2.34 (dd, $^2J_{HH}$ = 15.2, $^3J_{HH}$ = 10.3, 1H, C_eH_2,), 2.09 (dd, $^2J_{HH}$ = 15.2, $^3J_{HH}$ = 2.2, 1H, C_eH_2,), 1.50 (s, 9H, OC(CH_3)$_3$), 1.47 (s, 9H, OC(CH_3)$_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 171.2 (R*C*O$_2$C(CH$_3$)$_3$), 171.2 (R*C*O$_2$C(CH$_3$)$_3$), 145.4 (C_d), 133.0 (C_h), 128.6 (C_b), 127.5 (C_c), 125.7 (C_a), 119.1 (C_h), 82.0 (O*C*(CH$_3$)$_3$), 70.8 (*C*HOH), 57.7 (*C*(CO$_2$R)$_2$), 42.6 (C_e), 38.3 (C_f), 28.1 (OC(*C*H$_3$)$_3$), 28.1 (OC(*C*H$_3$)$_3$).

Enantiomeric ratio of 97:3 was determined using chiral SFC analysis (Whelk 01 column, 10% IPA/hexane – iso 10%, 4 mL/min, 125 bar): t_R = 7.0 [major, (S)], 9.7 [minor, (R)].



Area Percent	Area	Retention Time	Height
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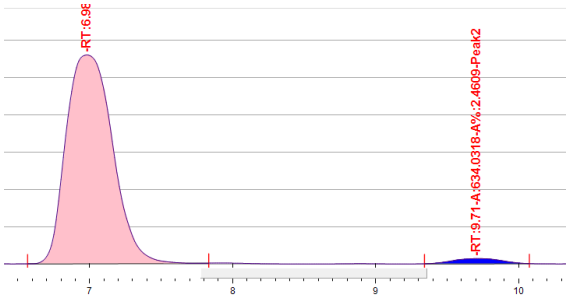
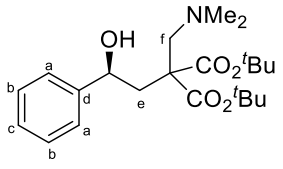
50.7508	18075.1679	11.01 min	960.8813



Area Percent	Area	Retention Time	Height
97.5391	25130.3774	6.98 min	1119.8161
2.4609	634.0318	9.71 min	27.5877

Di-*tert*-butyl (*S*)-2-((dimethylamino)methyl)-2-(2-hydroxy-2-phenylethyl)malonate, 117c'



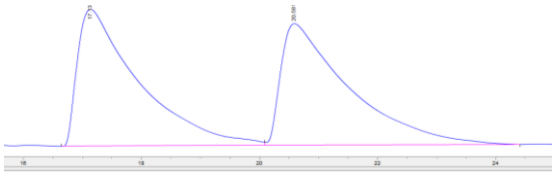
General procedure D using (*R*)-**94** (50 mg, 0.14 mmol, 1.0 equiv), phenyllithium (0.09 mL, 1.9 M solution in dibutyl ether, 1.2 equiv), dimethylmethylideneammonium iodide (50 mg, 0.27 mmol, 2.0

equiv), $MgBr_2 \cdot Et_2O$ (7.0 mg, 0.028 mmol, 0.2 equiv), a quantitative ^1H NMR yield was recorded of the product boronic ester (**117c**) before oxidation using general procedure A to yield **117c'** as a white solid (36 gm, 72% yield).

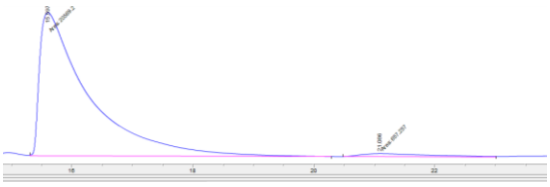
R_F 0.51 (60:40 petroleum ether/ethyl acetate); IR (film) ν_{max}/cm^{-1}: 3376, 3170, 2976, 2933, 2868, 2833, 2785, 1724, 1455, 1393, 1368, 1252, 1164, 1139; **HRMS** (ESI): Calcd. for $C_{22}H_{35}NO_5H^+$ ($[M+H]^+$) *m/z* 394.2588, found *m/z* 394.2602; $[\alpha]_D^{25}$ −1.4 (*c* = 1.62, 97:3 er);

^1H NMR ($CDCl_3$, 400 MHz) δ 7.39 (br. d, $^3J_{HH}$ = 7.3, 2H, C_aH), 7.32 (br. t, $^3J_{HH}$ = 7.3, 2H, C_bH), 7.22 (tt, $^3J_{HH}$ = 7.3, $^4J_{HH}$ = 1.3, 1H, C_cH), 4.73 (br. d, $^3J_{HH}$ = 9.6, 1H, C*H*(OH)(Ph)), 3.39 (d, $^2J_{HH}$ = 13.5, 1H, C_fH_2), 2.86 (d, $^2J_{HH}$ = 13.5, 1H, C_fH_2), 2.45 (dd, $^2J_{HH}$ = 15.5, $^3J_{HH}$ = 0.9, 1H, C_eH_2), 2.32 (dd, $^2J_{HH}$ = 15.5, $^3J_{HH}$ = 9.6, 1H, C_eH_2), 2.31 (s, 6H, $N(CH_3)_2$), 1.49 (s, 9H, $OC(CH_3)_3$), 1.44 (s, 9H, $OC(CH_3)_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 170.6 ($RCO_2C(CH_3)_3$), 169.7 ($RCO_2C(CH_3)_3$), 146.4 (C_d), 128.3 (C_b), 126.9 (C_c), 125.6 (C_a), 82.3 ($OC(CH_3)_3$), 82.2 ($OC(CH_3)_3$), 69.8 (*C*H(OH)(Ph)), 60.2 (C_f), 59.1 ($C(CO_2R)_2$), 45.7 ($N(CH_3)_2$), 42.8 (C_e), 28.0 ($OC(CH_3)_3$), 27.9 ($OC(CH_3)_3$).

Enantiomeric ratio of 97:3 was determined using chiral HPLC analysis (Chiralpak IA with guard, 3% IPA/hexane, 0.5 mL/min, 25 °C): t_R = 15.6 [major, (S)], 21.1 [minor, (R)].



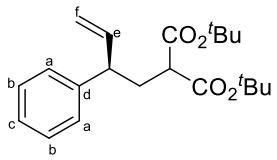
Time	Type	Area	Height	Width	Area%
17.131	BV	2502.9	34.7	0.9328	50.397
20.581	VB	2463.5	30.9	0.9476	49.603



Time	Type	Area	Height	Width	Area%
15.597	MM	20569.2	359	0.9548	96.904
21.086	MM	657.3	8	1.3612	3.096

6.2.10. Boronic ester transformations

Di-*tert*-butyl (*R*)-2-(2-phenylbut-3-en-1-yl)malonate, 120



Following a modified literature procedure:[68]

Tetravinyltin (61 µL, 0.34 mmol, 3.4 equiv) was added to a flame dried Schlenk flask and *n*-butyllithium (0.78 mL, 1.6 M solution in hexane, 13 equiv) was added dropwise at room temperature. The reaction was stirred at room temperature for 30 minutes and then the precipitate was left to settle for 30 minutes. The supernatant solvent was removed by syringe before the dropwise addition of anhydrous THF (1.2 mL) to give a 1.04 M solution of vinyllithium. Meanwhile, a flame dried Schlenk flask

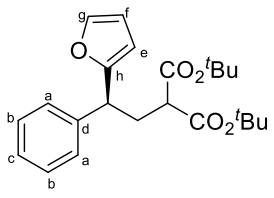
was charged with (*S*)-**110c** (44 mg, 0.099 mmol, 1.0 equiv) and anhydrous THF (0.3 mL) and cooled to −78 °C. A quarter of the vinyllithium solution (0.30 mL, 0.31 mmol, 3.2 equiv) was added dropwise at −78 °C before the reaction was warmed to room temperature and stirred for 30 minutes. After this time, the reaction was cooled to −78 °C before the addition of iodine (30 mg, 0.12 mmol, 1.2 equiv) in methanol (0.3 mL). After 20 minutes stirring at −78 °C, sodium methoxide (16 mg, 0.29 mmol, 3.0 equiv) was added as a suspension in methanol (0.1 mL). After 5 minutes, the reaction was warmed to room temperature and stirred for 1 h. Saturated aqueous sodium thiosulfate (1 mL) was added and after 5 minutes, water (10 mL) and diethyl ether (10 mL) were added and the phases separated. The aqueous phase was extracted with diethyl ether (3 × 10 mL) and the combined organic phases were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (100:0 → 80:20 hexane/ethyl acetate) to give **120** as a colourless oil (33 mg, 96% yield).

R_F 0.49 (90:10 petroleum ether/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 3062, 2977, 2932, 1741, 1725, 1637, 1478, 1393, 1368, 1281, 1255, 1163, 1139; **HRMS** (ESI): Calcd. for $C_{21}H_{30}O_4Na^+$ ($[M+Na]^+$) *m*/*z* 369.2036, found *m*/*z* 369.2046; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ −4.4 (*c* = 1.13, 97:3 er);

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.33–7.28 (m, 2H, C_bH), 7.23–7.19 (m, 3H, C_aH, C_cH), 5.94 (ddd, $^3J_{HH}$ = 17.5, 9.9, 7.8, 1H, C_eH), 5.11–5.06 (m, 2H, C_fH_2), 3.30 (br. q, $^3J_{HH}$ = 7.8, 1H, CH(Ph)(C_e)), 3.10 (t, $^3J_{HH}$ = 7.5, 1H, $CH(CO_2R)_2$), 2.27–2.16 (m, 2H, $CH_2CH(CO_2R)_2$), 1.47 (s, 9H, OC(CH_3)$_3$), 1.44 (s, 9H, OC(CH_3)$_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 169.0 ($RCO_2C(CH_3)_3$), 168.9 ($RCO_2C(CH_3)_3$), 143.2 (C_d), 141.0 (C_e), 128.7 (C_b), 127.8 (C_a), 126.7 (C_c), 115.3 (C_f), 81.5 (OC(CH_3)$_3$), 52.0 ($CH(CO_2R)_2$), 47.6 (CH(Ph)(C_e)), 34.4 ($CH_2CH(CO_2R)_2$), 28.1 (OC(CH_3)$_3$), 28.1 (OC(CH_3)$_3$).

Enantiomers not separable by chiral HPLC but expected enantiomeric ratio is 97:3, based on established enantiospecific nature of Zweifel olefination.[68]

Di-*tert*-butyl (*S*)-2-(2-(furan-2-yl)-2-phenylethyl)malonate, 121



Following a modified literature procedure:[71]

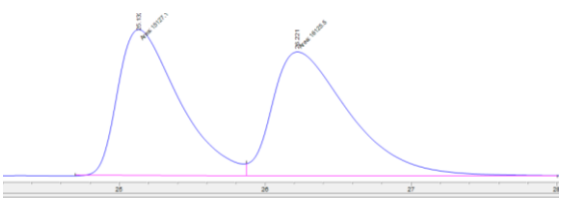
Furan (19.5 µL, 0.27 mmol, 2.4 equiv) was added to a flame dried Schlenk flask cooled to −78 °C followed by anhydrous THF (1 mL). *n*-Butyllithium (0.19 mL, 1.6 M solution in hexane, 2.7 equiv) was added and the reaction warmed to room temperature and stirred for 1 hour. The flask was

cooled to −78 °C before the addition of (*S*)-**110c** (50 mg, 0.11 mmol, 1.0 equiv) as a solution in anhydrous THF (0.5 mL). The reaction was stirred at −78 °C for 1 h. After this time, the solvent was removed *in vacuo* at 0 °C and replaced with dry methanol (1 mL) then cooled back to −78 °C. *N*-bromosuccinimide (24 mg, 0.13 mmol, 1.2 equiv) was then added as a solution in acetonitrile (1.5 mL) and anhydrous THF (1.5 mL) was also added. The reaction was stirred at −78 °C for 1 h. Saturated aqueous sodium thiosulfate (1 mL) was added and the reaction warmed to room temperature. Water (10 mL) and diethyl ether (10 mL) were added and the phases separated. The aqueous phase was extracted with diethyl ether (3 × 10 mL) and the combined organic phases were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (100:0 → 80:20 hexane/ethyl acetate) to give **121** as a colourless oil (26 mg, 61% yield).

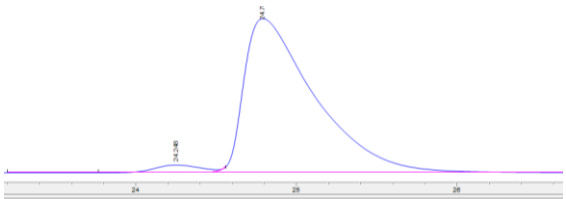
R_F 0.40 (90:10 petroleum ether/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 2977, 2933, 1741, 1724, 1586, 1478, 1455, 1368, 1257, 1160, 1137; **HRMS** (ESI): Calcd. for $C_{23}H_{30}O_5Na^+$ ($[M+Na]^+$) *m*/*z* 409.1985, found *m*/*z* 409.1995; $[\alpha]_D^{25}$ 27.3 (*c* = 1.20, 97:3 er);

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32 (dd, $^3J_{HH}$ = 1.9, $^4J_{HH}$ = 0.8, 1H, C_gH), 7.29 – 7.31 (m, 2H, C_bH), 7.25 – 7.23 (m, 3H, C_aH, C_cH), 6.29 (dd, $^3J_{HH}$ = 3.2, 1.9, 1H, C_fH), 6.11 (dt, $^3J_{HH}$ = 3.2, $^4J_{HH}$ = 0.8, 1H, C_eH), 4.01 (br. t, $^3J_{HH}$ = 8.0, 1H, C*H*(Ph)(Ar)), 3.05 (dd, $^3J_{HH}$ = 7.8, 7.2, 1H, C*H*($CO_2R)_2$), 2.59 (dt, $^2J_{HH}$ = 13.9, $^3J_{HH}$ = 7.8, 1H, CH_2CH($CO_2R)_2$), 2.40 (ddd, $^2J_{HH}$ = 13.9, $^3J_{HH}$ = 8.4, 7.2, 1H, CH_2CH($CO_2R)_2$), 1.47 (s, 9H, OC($CH_3)_3$), 1.44 (s, 9H, OC($CH_3)_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 169.0 (R*C*O_2C($CH_3)_3$), 168.7 (R*C*O_2C($CH_3)_3$), 156.7 (C_h), 141.8 (C_g), 141.6 (C_d), 128.7 (C_b), 128.1 (C_a), 127.0 (C_c), 110.2 (C_f), 106.0 (C_e), 81.7 (O*C*($CH_3)_3$), 81.6 (O*C*($CH_3)_3$), 52.0 (*C*H($CO_2R)_2$), 43.0 (*C*H(Ph)(Ar)), 33.8 (CH_2CH($CO_2R)_2$), 28.1 (OC(*C*$H_3)_3$), 28.1 (OC(*C*$H_3)_3$).

Enantiomeric ratio of 97:3 was determined using chiral HPLC analysis (Chiralpak IB with guard + IB without guard, 0.5% IPA/hexane, 0.4 mL/min, 0 °C): t_R = 24.2 [minor, (R)], 24.8 [major, (S)].

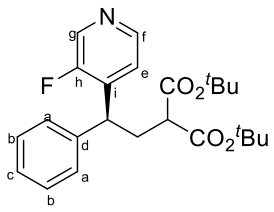


Time	Type	Area	Height	Width	Area%
25.132	MF	15127.1	516.5	0.4881	48.403
26.221	FM	16125.5	438	0.6136	51.597



Time	Type	Area	Height	Width	Area%
24.248	VV E	928.8	46.5	0.3115	3.151
24.788	VV R	28549.7	930.9	0.4543	96.849

Di-*tert*-butyl (*S*)-2-(2-(3-fluoropyridin-4-yl)-2-phenylethyl)malonate, 122



Following a modified literature procedure:[72]

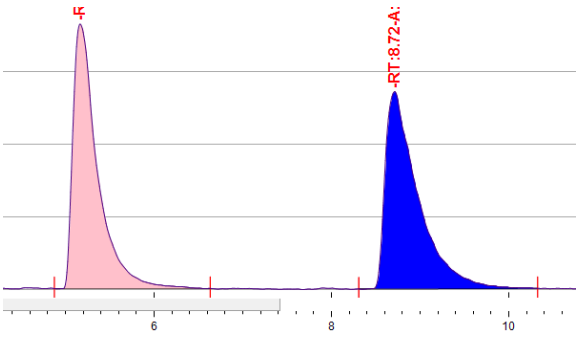
A flame dried Schlenk flask was charged with diisopropylamine (39 µL, 0.28 mmol, 2.5 equiv) and anhydrous THF (0.56 mL) and cooled to −78 °C. *n*-Butyllithium (0.19 mL, 1.6 M solution in hexane, 2.7 equiv) was added and the reaction was stirred at −78 °C for 1 hour. After this time, a solution of 3-fluoropyridine (24 µL, 0.28 mmol, 2.5 equiv) in anhydrous THF (0.4 mL) was added dropwise and the reaction stirred at −78 °C for 30 minutes. Next, a solution of (*S*)-**110c** (50 mg, 0.11 mmol, 1.0 equiv) in anhydrous THF (0.5 mL) was added and the reaction stirred at −78 °C for 1.5 h. After this time, 2,2,2-trichloroethyl chloroformate (100 µL, 0.73 mmol, 6.5 equiv) was added dropwise. The reaction was stirred at −78 °C for 2 h then warmed to room temperature and stirred for an additional 16 h. Water (10 mL) and diethyl ether (10 mL) were added and the phases separated. Saturated aqueous sodium bicarbonate was added to the aqueous phase which was then extracted with diethyl ether (3 × 10 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude mixture was dissolved in THF (1 mL) and cooled to 0 °C. In air, a solution of 2 M NaOH/30% $H_2O_{2(aq)}$ (1 mL, 1:1 v/v) was added dropwise and the reaction was then stirred at room temperature for 18 h. Water (10 mL) and diethyl ether (10 mL) were added and the phases separated. Saturated aqueous sodium bicarbonate was added to the aqueous phase which was then extracted with diethyl ether (3 × 10 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (100:0 → 60:40 hexane/ethyl acetate) to give **122** as a colourless oil (23 mg, 50% yield).

R_F 0.49 (60:40 petroleum ether/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 2978, 2932, 1740, 1725 (C=O), 1600, 1490, 1455, 1369, 1247, 1163, 1139; **HRMS** (ESI): Calcd. for $C_{24}H_{30}FNO_4H^+$ ($[M+H]^+$) *m*/*z* 416.2232, found *m*/*z* 416.2238; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ 11.6 (*c* = 1.00, 96:4 er);

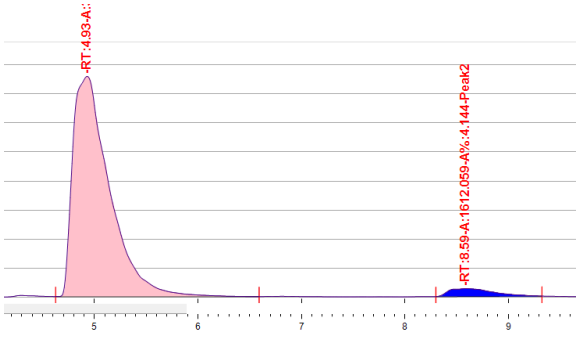
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.37 – 8.34 (m, 2H, C_fH, C_gH), 7.33 – 7.29 (m, 2H, C_bH), 7.27 – 7.22 (m, 4H, C_aH, C_cH, C_eH), 4.31 (t, $^3J_{HH}$ = 8.1, 1H, C*H*(Ph)(Ar)), 3.01 (dd, $^3J_{HH}$ = 8.0, 7.0, 1H, C*H*($CO_2R)_2$), 2.63 – 2.49 (m, 2H, $CH_2CH(CO_2R)_2$), 1.46 (s, 9H, OC($CH_3)_3$),1.44 (s, 9H, OC($CH_3)_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 168.4 ($RCO_2C(CH_3)_3$), 157.9 (d, $^1J_{CF}$ = 255.3, C_h), 140.6 (C_d), 146.1 (d, $^4J_{CF}$ = 5.1, C_f), 139.5 (d, $^2J_{CF}$ = 12.1, C_i), 138.3 (d, $^2J_{CF}$ = 25.1, C_g), 129.0 (C_b), 128.1 (C_a), 127.4 (C_c), 122.9 (d, $^3J_{CF}$ = 1.2, C_e), 82.0 (O*C*($CH_3)_3$), 82.0 (O*C*($CH_3)_3$), 52.0

(*C*H(CO$_2$R)$_2$), 40.9 (d, $^3J_{CF}$ = 1.8, *C*H(Ph)(Ar)), 32.9 (*C*H$_2$CH(CO$_2$R)$_2$), 28.0 (OC(*C*H$_3$)$_3$), 28.0 (OC(*C*H$_3$)$_3$); **^{19}F NMR** (CDCl$_3$, 377 MHz) δ −131.4 (br. d, $^3J_{HF}$ = 6.2, C$_h$*F*).

Enantiomeric ratio of 96:4 was determined using chiral SFC analysis (Chiralpak IB, 10% IPA/hexane – iso 10%, 4 mL/min, 125 bar): t_R = 4.9 [major, (S)], 8.6 [minor, (R)].

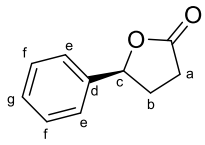


Area Percent	Area	Retention Time	Height
50.113	3481.4088	5.17 min	182.2636
49.887	3465.7083	8.72 min	135.8914



Area Percent	Area	Retention Time	Height
95.856	37289.0596	4.93 min	1517.3483
4.144	1612.059	8.59 min	54.901

(*S*)-5-phenyldihydrofuran-2(3H)-one, **123**



Following a modified literature procedure:[91]

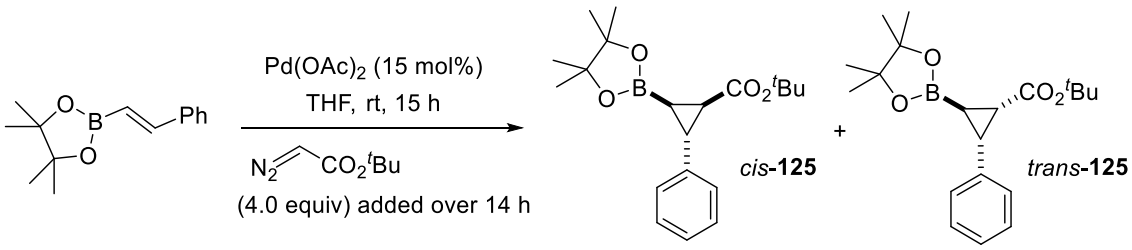
Formic acid (7.9 mL) was added to round bottom flask containing (*S*)-**111c** (0.27 g, 0.79 mmol) and the reaction was stirred at room temperature until complete consumption of the starting material was observed by TLC (5.5 hours). After this time, water (10 mL) and diethyl ether (10 mL) were added and the phases separated. The aqueous phase was extracted with diethyl ether (3 × 10 mL) and the combined organic phases were washed with brine, dried dried (MgSO$_4$), filtered and concentrated under reduced pressure. The mixture was dissolved in toluene and heated to reflux for 14 hours. After this time, the reaction mixture was concentrated to an approximate volume of 2 mL and then loaded directly onto a preequilibrated silica gel column and purified by flash chromatography (100:0 → 0:100 pentane/diethyl ether) to give **123** as a colourless oil (96 mg, 75% yield);

R$_F$ 0.20 (80:20 petroleum ether/ethyl acetate); $[\alpha]_D^{25}$ −32.7 (*c* = 3.18, 97:3 er);

^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.42 – 7.32 (m, 5H, C$_e$*H*, C$_f$*H*, C$_g$*H*), 5.54 – 5.50 (m, 1H, C$_c$*H*), 2.71 – 2.62 (m, 3H, C$_b$*H*$_2$, C$_a$*H*$_2$), 2.17 – 2.14 (m, 1H, C$_b$*H*$_2$); **^{13}C NMR** (CDCl$_3$, 101 MHz) δ 177.0 (*C*=O), 139.5 (*C*$_d$), 128.9 (*C*$_e$), 128.6 (*C*$_g$), 125.4 (*C*$_f$), 81.4 (*C*$_c$), 31.1 (*C*$_a$), 29.1 (*C*$_b$). All characterisation data is consistent with that reported in the literature.[92]

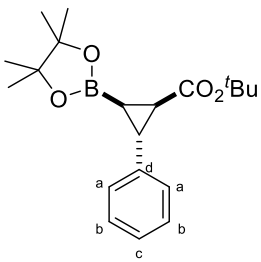
6.2.11. Starting material synthesis for reactivity study

***tert*-Butyl 2-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropane-1-carboxylate, *cis*-125 and *trans*-125**



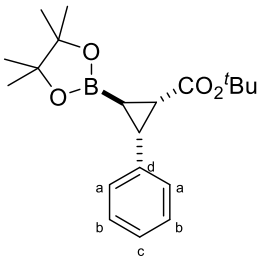
Following a modified literature procedure:[95]

A flame dried Schlenk flask charged with *trans*-2-phenyl vinyl boronic acid pinacol ester (0.56 g, 2.45 mmol, 1.0 equiv) and $Pd(OAc)_2$ (55 mg, 0.24 mmol, 0.1 equiv) was evacuated and purged with nitrogen. Anhydrous THF (20 mL) was added and, with stirring, a solution of *tert*-butyl diazo acetate (1.36 mL, 9.79 mmol, 4.0 equiv) in anhydrous THF (4.5 mL) was added over 14 hours by syringe pump at room temperature. After half of the addition, a further portion of $Pd(OAc)_2$ (30 mg, 0.13 mmol, 0.05 equiv) was added. The reaction mixture was then stirred for a further 2 hours at room temperature. The solvent was removed *in vacuo* and the crude mixture was added to a pre-equilibrated column (98:2 pentane/ethyl acetate, 25 g Biotage ULTRA cartridge) with petroleum ether (2 × 0.5 mL) and eluted (98:2 → 80:20 pentane/ethyl acetate) to separate the two diastereomers that were assigned as *cis*/*trans* using NOE data. *cis*-**125** eluted first and was isolated as a white amorphous solid (238 mg, 28% yield). *trans*-**125** eluted second and was isolated as a white amorphous solid (279 mg, 33% yield).



R_F 0.57 (90:10 petroleum ether/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 2977, 2934, 1709, 1460, 1437, 1381, 1367 (B-O), 1317, 1209; **HRMS** (ESI): Calcd. for $C_{20}H_{29}BO_4$ *m*/*z* 344.2159, Neither $[M]^+$ or $[M+Na]^+$ was found, **LRMS** found *m*/*z* 217.1 fragment $[M - Bpin]^+$;

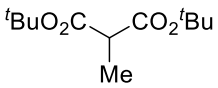
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.26 (t, $^3J_{HH}$ = 7.4, 2H, C_bH), 7.17 (tt, $^3J_{HH}$ = 7.4, $^4J_{HH}$ = 1.4, 1H, C_cH), 7.11 (br. d, $^3J_{HH}$ = 7.4, 2H, C_aH), 2.60 (dd, $^3J_{HH}$ = 7.9, 4.4, 1H, C*H*Ph), 2.01 (dd, $^3J_{HH}$ = 9.7, 4.4, 1H, C*H*(CO_2R)), 1.45 (s, 9H, OC(CH_3)$_3$), 1.31 (s, 6H, pinacol CH_3), 1.28 (s, 6H, pinacol CH_3), 0.87 (dd, $^3J_{HH}$ = 9.7, 7.9, 1H, C*H*Bpin); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 172.4 (R*C*O_2C(CH_3)$_3$), 141.1 (C_dH), 128.5 (C_bH), 126.3 (C_cH), 126.1 (C_aH), 83.8 (pinacol O*C*(R)(CH_3)$_2$), 80.9 (O*C*(CH_3)$_3$), 30.1 *C*H(CO_2R), 28.6 (*C*HPh), 28.3 (OC(*C*H_3)$_3$), 25.2 (pinacol *C*H_3), 25.0 (pinacol *C*H_3); **^{11}B NMR** ($CDCl_3$, 128 MHz) δ 30.7.



R$_F$ 0.42 (90:10 petroleum ether/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 2976, 2935, 1726, 1707, 1437, 1366, 1325, 1289; **HRMS** (ESI): Calcd. for $C_{20}H_{29}BO_4$ *m*/*z* 344.2159, Neither $[M]^+$ or $[M+Na]^+$ was found, **LRMS** found *m*/*z* 217.1 fragment $[M - Bpin]^+$;

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.30 – 7.23 (m, 4H, C$_a$*H*, C$_b$*H*), 7.18 (tt, $^3J_{HH}$ = 7.3, $^4J_{HH}$ = 1.5, 1H, C$_c$*H*), 2.67 (br. t, $^3J_{HH}$ = 8.5, 1H, C*H*Ph), 2.13 (dd, $^3J_{HH}$ = 9.2, 6.1, 1H, C*H*(CO$_2$R)), 1.31 (dd, $^3J_{HH}$ = 7.7, 6.1, 1H, C*H*Bpin), 1.26 (s, 12H, pinacol C*H*$_3$), 1.11 (s, 9H, OC(C*H*$_3$)$_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 169.9 (R*C*O$_2$C(CH$_3$)$_3$), 137.0 (C$_d$*H*), 129.6 (C$_a$*H* or C$_b$*H*), 127.9 (C$_a$*H* or C$_b$*H*), 126.6 (C$_c$*H*), 83.8 (pinacol O*C*(R)(CH$_3$)$_2$), 80.3 (O*C*(CH$_3$)$_3$), 30.0 (*C*HPh), 28.1 (C*H*(CO$_2$R)), 27.9 (OC(*C*H$_3$)$_3$), 24.9 (pinacol *C*H$_3$); **^{11}B NMR** ($CDCl_3$, 128 MHz) δ 31.8.

Di-*tert*-butyl 2-methylmalonate, 130

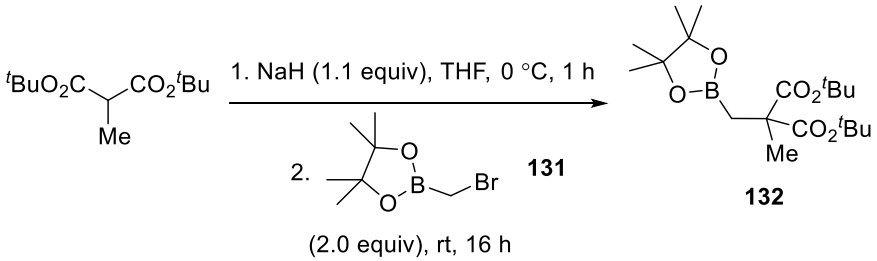


Following a modified literature procedure:[164]

A flame dried Schlenk flask was charged with sodium hydride (0.105 g, 60% dispersion in mineral oil, 2.63 mmol), evacuated and flushed with nitrogen. Anhydrous THF (5 mL) was added before the dropwise addition of di-*tert*-butyl malonate (0.56 mL, 2.50 mmol) with stirring. The reaction was stirred at room temperature for 30 minutes. After this time, methyl iodide (0.16 mL, 2.51 mmol) was added dropwise and the reaction stirred overnight at room temperature. The reaction was quenched with saturated ammonium chloride solution (2 mL). Water (20 mL) and diethyl ether (20 mL) were added and the phases separated. The aqueous phase was extracted with diethyl ether (3 × 20 mL) and the combined organic phases were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude reaction mixture was purified by flash chromatography (100:0 → 90:10 pentane/ethyl acetate) to give **130** as a colourless oil (0.366 g, 64% yield).

R$_F$ 0.44 (90:10 petroleum ether/ethyl acetate); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 3.22 (q, $^3J_{HH}$ = 7.2, 1H, CH$_3$C*H*(CO$_2$R)$_2$), 1.46 (s, 18H, OC(C*H*$_3$)$_3$), 1.32 (d, $^3J_{HH}$ = 7.2, 3H, C*H*$_3$CH(CO$_2$R)$_2$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 169.8 (*C*=O), 81.4 (O*C*(CH$_3$)$_3$), 48.4 (CH$_3$*C*H(CO$_2$R)$_2$), 28.1 (OC(*C*H$_3$)$_3$), 13.6 (*C*H$_3$CH(CO$_2$R)$_2$). All characterisation data is consistent with that reported in the literature.[164]

Di-*tert*-butyl 2-methyl-2-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)malonate, 132



Following a modified literature procedure:[97]

A flame dried Schlenk flask was charged with sodium hydride (20 mg, 60% dispersion in mineral oil, 0.50 mmol), evacuated and flushed with nitrogen. Anhydrous THF (1 mL) was added and the flask cooled to 0 °C. A solution of di-*tert*-butyl 2-methylmalonate (90 mg, 0.39 mmol) in anhydrous THF (1 mL) was then added dropwise with stirring. The reaction was then stirred at room temperature for 1 hour. After this time, 2-(bromomethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**131**) (0.14 mL, 0.79 mmol) was added dropwise and the reaction stirred overnight at room temperature. The reaction was quenched with saturated ammonium chloride solution (2 mL). Water (10 mL) and diethyl ether (10 mL) were added and the phases separated. The aqueous phase was extracted with diethyl ether (3 × 20 mL) and the combined organic phases were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude reaction mixture was purified by flash chromatography (100:0 → 90:10 pentane/ethyl acetate) to give **132** as a colourless oil (22 mg, 15% yield).

R_F 0.33 (90:10 petroleum ether/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 2977, 2934, 1724, 1479, 1367, 1325, 1251, 1145; **HRMS** (ESI): Calcd. for $C_{19}H_{35}O_6BNa^+$ ($[M+Na]^+$) *m*/*z* 393.2419, found *m*/*z* 393.2438;

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.44 (s, 3H, C*H*$_3$CR(CO_2R)$_2$)), 1.43 (s, 18H, OC(C*H*$_3$)$_3$), 1.23 (s, 13H, pinacol C*H*$_3$, C*H*Bpin); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 172.7 (*C*=O), 83.2 (pinacol O*C*(R)(CH_3)$_2$), 80.8 (O*C*(CH_3)$_3$), 53.1 (CH_3*C*R(CO_2R)$_2$), 28.0 (OC(*C*H_3)$_3$), 24.9 (pinacol *C*H_3), 21.7 (*C*H_3CR(CO_2R)$_2$); **^{11}B NMR** ($CDCl_3$, 128 MHz) δ 31.7.

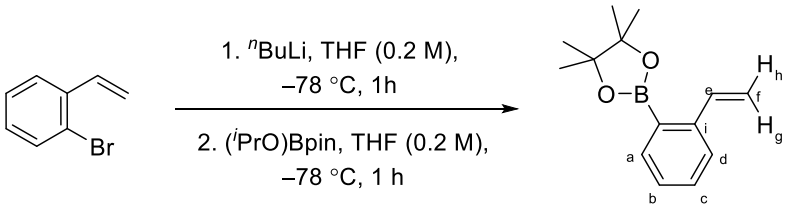
6.2.12. Conditions for the ^{11}B NMR analysis to study the reactivity of different β-carbonyl boronate complexes with $MgBr_2 \cdot Et_2O$

A flame dried Schlenk flask was charged with the boronic ester (**94**, *trans*-**125** or **132**, 1.0 equiv), evacuated and purged with nitrogen before the addition of anhydrous THF

(0.15 M). The reaction flask was cooled to at −78 °C before the dropwise addition of *n*-butyllithium (1.1 equiv) and the reaction was then stirred at −78 °C for 1 hour. After this time, a 0.3 mL aliquot of the reaction mixture was transferred to a quartz NMR tube under an inert atmosphere of nitrogen. The NMR tube was sealed with a septum and a ^{11}B NMR spectrum was recorded. The aliquot was transferred back to the original reaction flask before the addition of $MgBr_2.Et_2O$ (1.5 equiv) at −78 °C. The reaction was stirred overnight whilst warming slowly to room temperature. After this time another ^{11}B NMR spectrum was recorded using the same method. The aliquot was then transferred back to the original reaction flask before the addition of water (10 mL) and diethyl ether (10 mL). The phases were separated and the aqueous phase was extracted with diethyl ether (3 × 10 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. A crude ^{1}H NMR spectrum was then recorded. In both reactions with boronic esters *trans*-**125** and **132**, there was no evidence of the 1,2-metallate shift boronic ester product in the crude ^{1}H NMR spectrum. Due to instability, borinic esters *trans*-**128** and **2.45** could not be isolated.

6.2.13. Attempted deraromative 1,2-metallate rearrangement reaction

4,4,5,5-Tetramethyl-2-(2-vinylphenyl)-1,3,2-dioxaborolane, 143

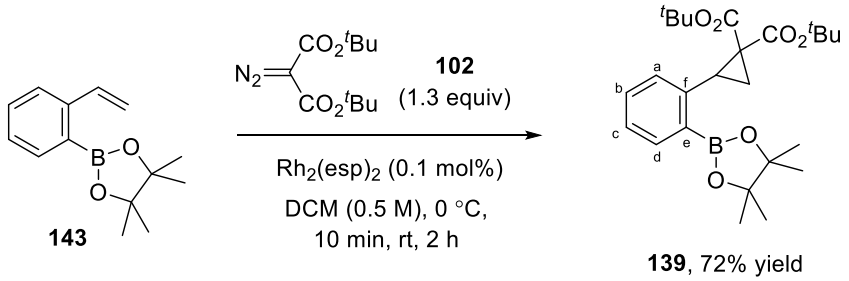


A flame dried Schlenk tube, evacuated and purged with nitrogen, was charged with 2-bromostyrene (0.68 mL, 5.46 mmol, 1 eq.). THF (27 mL, 0.2 M) was added and the solution was cooled to –78 °C. *n*-Butyllithium (3.76 mL, 1.6 M solution in hexane, 1.1 eq.), was added and the reaction was stirred at –78 °C for 1 hour. After this time, 2-Isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (^{i}PrOBpin) (1.34 mL, 6.56 mmol, 1.2 eq.) was added dropwise at –78 °C and the reaction was stirred at –78 °C for 1 hour. After this time, water (50 mL) was added and the phases separated. The aqueous phase was extracted with diethyl ether (3 × 30 mL) and the combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (100:0 → 90:10 pentane/ethyl acetate) to yield **143** as a white solid (1.23 g, 97% yield).

R_F 0.59 (90:10 petroleum ether/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 3086, 3057, 2981, 2930, 1626, 1594, 1560, 1482, 1444, 1379, 1341, 1261; **HRMS** (ESI): Calcd. for $C_{14}H_{19}BO_2Na^+$ ($[M+Na]^+$) *m*/*z* 253.1370, found *m*/*z* 253.1371;

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.80 (dd, $^3J_{HH}$ = 7.5, $^4J_{HH}$ = 1.0, 1H, C_aH), 7.63 (br. d, $^3J_{HH}$ = 7.5, 1H, C_dH), 7.53 (dd, $^3J_{HH}$ = 17.5, 11.0, 1H, C_eH), 7.40 (br. dt, $^3J_{HH}$ = 7.5, $^4J_{HH}$ = 1.4, 1H, C_cH), 7.25 (dt, $^3J_{HH}$ = 7.5, $^4J_{HH}$ = 1.1, 1H, C_bH), 5.70 (dd, $^3J_{HH}$ = 17.5, $^2J_{HH}$ = 1.4, 1H, C_fH_g), 5.27 (dd, $^3J_{HH}$ = 11.0, $^2J_{HH}$ = 1.4, 1H, C_fH_h), 1.36 (s, 12H, pinacol CH_3); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 143.9 (C_i), 137.7 (C_e), 136.1 (C_a), 131.1 (C_c), 126.9 (C_b), 124.6 (C_d), 114.7 (C_f), 83.8 (pinacol O*C*(R)(CH_3)$_2$), 25.0 (pinacol *C*H_3); **^{11}B NMR** ($CDCl_3$, 128 MHz) δ 30.2.

Di-*tert*-butyl 2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclopropane-1,1-dicarboxylate, 139

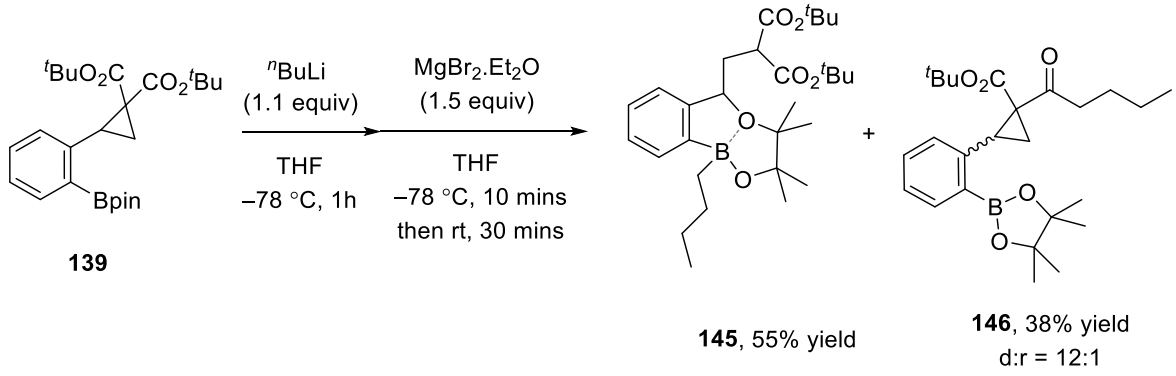


A flame dried Schlenk tube was charged with $Rh_2(esp)_2$ (2 mg, 0.003 mmol, 0.1 mol%), evacuated and purged with nitrogen before the addition of DCM (2 mL). DCM (0.8 mL) was added to a separate vial containing **143** (0.600 g, 2.61 mmol, 1.0 equiv) and this solution was added to the reaction flask. Additional DCM (2 × 0.2 mL) was used to wash residual **143** from the vial into the reaction mixture. Di-*tert*-butyl 2-diazomalonate (**102**) (0.821 g, 3.39 mmol, 1.3 equiv) was added at 0 °C as a solution in DCM (2 mL). The reaction was stirred at 0 °C for 10 minutes then at room temperature for 2 hours. After this time, water (30 mL) was added and the phases separated. The aqueous phase was extracted with DCM (3 × 30 mL) and the combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (100:0 → 90:10 pentane/ethyl acetate) to yield **139** as a white solid (0.837 g, 72% yield).

R_F 0.37 (90:10 petroleum ether/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 2979, 2932, 1728, 1711, 1600, 1479, 1444, 1368, 1349, 1332, 1317, 1289, 1258, 1220; **HRMS** (ESI): Calcd. for $C_{25}H_{37}BO_6Na^+$ ($[M+Na]^+$) *m*/*z* 467.2575, found *m*/*z* 467.2602.

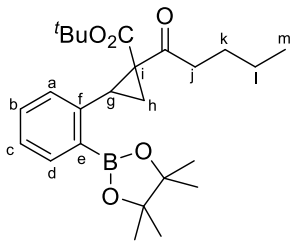
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.77 (dd, $^3J_{HH}$ = 7.5, $^4J_{HH}$ = 1.5, 1H, C_dH), 7.31 (td, $^3J_{HH}$ = 7.5, $^4J_{HH}$ = 1.5, 1H, C_bH), 7.19 (td, $^3J_{HH}$ = 7.5, $^4J_{HH}$ = 1.1, 1H, C_cH), 7.04 (br. d, $^3J_{HH}$ = 7.5, 1H, C_aH), 3.78 (dd, $^3J_{HH}$ = 8.3, 1H, C*H*(Ar)), 2.10 (dd, $^3J_{HH}$ = 8.3, $^2J_{HH}$ = 5.0, 1H, $CH_2C(CO_2R)_2$), 1.51 – 1.48 (m, 1H, $CH_2C(CO_2R)_2$), 1.49 (s, 9H, $OC(CH_3)_3$), 1.33 (s, 12H, pinacol CH_3), 1.00 (s, 9H, $OC(CH_3)_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 169.3 ($RCO_2C(CH_3)_3$), 166.3 ($RCO_2C(CH_3)_3$), 140.8 (C_f), 135.8 (C_d), 130.7 (C_c), 126.7 (C_a), 126.4 (C_b), 83.7 (pinacol $OC(R)(CH_3)_2$), 81.2 ($OC(CH_3)_3$), 80.6 ($OC(CH_3)_3$), 39.7 ($C(CO_2R)_2$), 31.1 (*C*H(Ar)), 28.4 ($OC(CH_3)_3$), 27.5 ($OC(CH_3)_3$), 25.1 (pinacol CH_3), 24.8 (pinacol CH_3), 17.9 ($CH_2C(CO_2R)_2$); **^{11}B NMR** ($CDCl_3$, 128 MHz) δ 30.6.

Di-*tert*-butyl -2-((1-butyl-3,3,4,4-tetramethyl-1,3,4,6-tetrahydrobenzo[c][1,6,2]dioxaborocin-6-yl)methyl)malonate, 145, and *tert*-butyl 1-pentanoyl-2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclopropane-1-carboxylate, 146



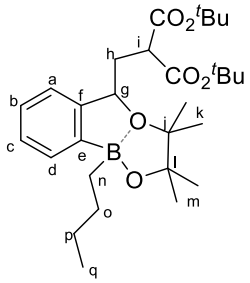
A flame dried Schlenk flask was charged with **139** (89 mg, 0.20 mmol, 1.0 equiv), evacuated and purged with nitrogen before the addition of anhydrous THF (1 mL). The reaction flask was cooled to at −78 °C before the dropwise addition of *n*-butyllithium (0.12 mL, 1.8 M solution in hexane, 1.1 equiv.). The reaction was then stirred at −78 °C for 1 hour. $MgBr_2.Et_2O$ (77 mg, 0.30 mmol, 1.5 equiv) was added as a solid under a positive flow of nitrogen at −78 °C and the reaction stirred at this temperature for 10 minutes then warmed to room temperature for 30 minutes. After this time, water (10 mL) and ethyl acetate (10 mL) were added and the phases separated. The aqueous phase was extracted with ethyl acetate (3 × 10 mL) and the combined organic phases were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. A quantitative ^{1}H NMR spectrum was recorded with dibromomethane as an internal standard. The crude mixture was purified by flash column chromatography (100:0 →

80:20 pentane/ethyl acetate) to yield **145** (16 mg, 16% isolated yield) as a white solid and **146** (21 mg, 25% isolated yield) as a white solid.



R_F 0.45 (90:10 pentane/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 2976, 2931, 1703, 1599, 1445, 1368, 1348, 1316, 1280, 1258, 1149; **HRMS** (ESI): Calcd. for $C_{25}H_{37}BO_5Na^+$ ([M+Na]$^+$) *m*/*z* 451.2631, found *m*/*z* 451.2647.

Major diastereomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.76 (dd, $^3J_{HH}$ = 7.5, $^4J_{HH}$ = 1.6, 1H, C_dH), 7.31 (td, $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.6, 1H, C_bH), 7.19 (td, $^3J_{HH}$ = 7.4, $^4J_{HH}$ = 1.1, 1H, C_cH), 6.91 (d, $^3J_{HH}$ = 7.4, 1H, C_aH), 3.74 (dd, $^3J_{HH}$ = 8.6, 8.6, 1H, C_gH), 2.70 (ddd, $^2J_{HH}$ = 17.2, $^3J_{HH}$ = 9.2, 5.7, 1H, C_JH_2), 2.31 (dd, $^3J_{HH}$ = 8.3, 4.7, 1H, C_hH_2), 1.81 (ddd, $^2J_{HH}$ = 17.2, $^3J_{HH}$ = 9.3, 5.6, 1H, C_jH_2), 1.53 – 1.50 (m, 10H, OC(CH_3)$_3$, C_hH_2), 1.36 (s, 6H, pinacol CH_3), 1.36 (s, 6H, pinacol CH_3), 1.23 – 1.11 (m, 1H, C_kH_2), 0.96 – 0.84 (m, 2H, C_lH_2), 0.86 – 0.76 (m, 1H, C_kH_2), 0.67 (t, $^3J_{HH}$ = 7.2, 3H, C_mH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 203.6 (C_iC(O)C_j), 169.7 (R*C*O$_2$C(CH$_3$)$_3$), 140.0 (*C*$_f$), 136.1 (*C*$_d$), 131.0 (*C*$_b$), 126.7 (*C*$_a$), 126.5 (*C*$_c$), 83.9 (pinacol O*C*(R)(CH$_3$)$_2$), 81.7 (O*C*(CH$_3$)$_3$), 46.0 (*C*$_i$), 42.4 (*C*$_j$), 33.7 (*C*$_g$), 28.4 (OC(*C*H$_3$)$_3$), 25.5 (*C*$_k$), 25.1 (pinacol *C*H$_3$), 24.8 (pinacol *C*H$_3$), 22.2 (*C*$_l$), 17.4 (*C*$_h$), 13.9 (*C*$_m$); **^{11}B NMR** ($CDCl_3$, 128 MHz) δ 30.4.

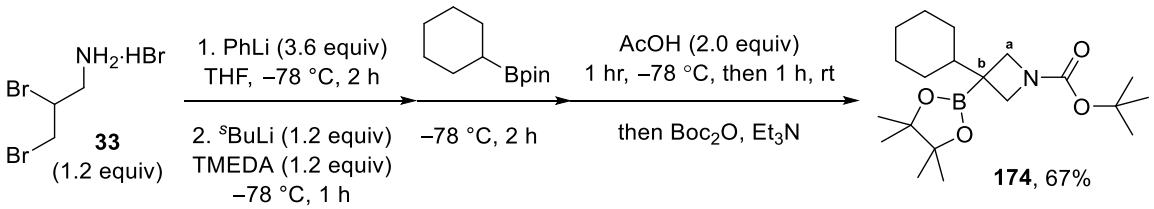


R_F 0.27 (90:10 pentane/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 2977, 2937, 1726, 1457, 1359, 1275, 1239, 1139; **HRMS** (ESI): Calcd. for $C_{29}H_{47}BO_6Na^+$ ([M+Na]$^+$) *m*/*z* 525.3363, found *m*/*z* 525.3366.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.32 (m, 1H, C_dH), 7.20 – 7.15 (m, 2H, C_bH, C_cH), 7.05 – 7.00 (m, 1H, C_aH), 5.31 (dd, $^3J_{HH}$ = 10.1, 3.5, 1H, C_gH), 3.41 (dd, $^3J_{HH}$ = 10.7, 4.0, 1H, C_iH), 2.35 (ddd, $^2J_{HH}$ = 14.4, $^3J_{HH}$ = 10.7, 3.5, 1H, C_hH), 2.11 (ddd, $^2J_{HH}$ = 14.4, $^3J_{HH}$ = 10.1, 4.0, 1H, C_hH), 1.51 (s, 9H, OC(CH_3)$_3$), 1.43 (br. s, 12H, OC(CH_3)$_3$, C_kH_3), 1.32 – 1.25 (m, 4H, C_oH_2, C_pH_2), 1.24 (s, 3H, C_mH_3), 1.22 (s, 3H, C_kH_3), 0.83 (t, $^3J_{HH}$ = 7.0, 3H, C_qH_3), 0.77 – 0.67 (m, 5H, C_mH_3, C_nH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.5 (R*C*O$_2$C(CH$_3$)$_3$), 168.4 (R*C*O$_2$C(CH$_3$)$_3$), 142.7 (*C*$_f$), 129.1 (*C*$_d$), 127.4 (*C*$_c$), 126.3 (*C*$_b$), 121.1 (*C*$_a$), 91.5 (*C*$_j$), 82.2 (O*C*(CH$_3$)$_3$), 82.1 (O*C*(CH$_3$)$_3$), 80.8 (*C*$_g$), 79.6 (*C*$_l$), 50.9 (*C*$_i$), 37.4 (*C*$_h$), 28.1 (OC(*C*H$_3$)$_3$), 28.0 (OC(*C*H$_3$)$_3$), 28.0 (*C*$_p$), 27.1 (*C*$_m$), 26.6 (*C*$_o$), 25.8 (*C*$_m$), 25.3 (*C*$_m$), 24.8 (br., *C*$_n$), 20.3 (*C*$_m$), 14.2 (*C*$_q$); **^{11}B NMR** ($CDCl_3$, 128 MHz) δ 26.1.

6.3. Synthetic procedures for chapter 3

6.3.1. One pot formation of azabicyclo[1.1.0]butane and lithiation/borylation with cyclohexyl pinacol boronic ester

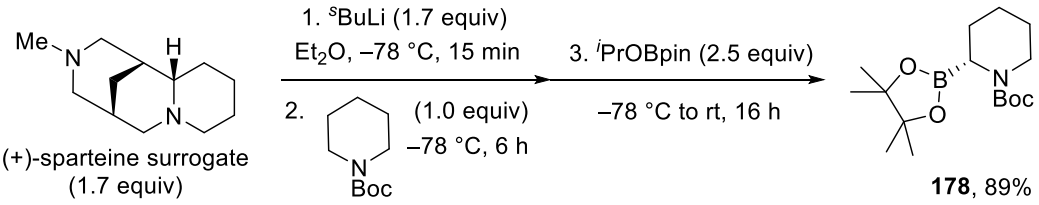


Phenyllithium (in Bu_2O, 0.87 mmol, 3.6 equiv) was added dropwise (at a rate of 0.02 mL/min) to a suspension of salt **33**[A] (85 mg, 0.29 mmol, 1.2 equiv) in anhydrous THF (0.9 mL) at –78 °C (dry ice/acetone). After complete addition, the resulting solution was stirred for a further 2 hours at –78 °C. TMEDA (40 μL, 0.29 mmol, 1.2 equiv) and *sec*-butyllithium (in hexane, 0.29 mmol, 1.2 equiv) were then added dropwise, and the resulting solution stirred for 1 hour at –78 °C. Cyclohexyl pinacol boronic ester (50 mg, 0.24 mmol, 1.0 equiv) in anhydrous THF (0.5 mL) was then added dropwise and the mixture was stirred for 2 hours. Acetic acid (30 μL, 0.48 mmol, 2.0 equiv) was then added dropwise and the mixture is stirred for 1 hour at –78 °C (dry ice/acetone) then warmed to ambient temperature and stirred for a further 1 hour. Triethylamine (0.14 mL, 0.96 mmol, 4.0 equiv) and di-*tert*-butyl dicarbonate (0.1 mL, approx. 0.5 mmol, approx. 2.0 equiv) were finally added and the resulting mixture was stirred overnight. Et_2O (15 mL) and HCl (1 m aqueous solution, 5 mL) were then added. The mixture was extracted with Et_2O (3× 10 mL) and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (90:10 pentane/ethyl acetate) to yield **174** (59 mg, 67% yield) as a white solid.

Notes: (A) Salt **33** was synthesised according to a reported procedure.[28]

R_F = 0.25 (90:10 pentane/ethyl acetate); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.91 (d, $^2J_{HH}$ = 7.8, 2H, 2 × C_aH), 3.63 (br. d, $^2J_{HH}$ = 7.8, 2H, 2 × C_aH), 1.74 – 1.62 (m, 6H, 3 × CH_2), 1.50 – 1.41 (m, 1H, C*H*), 1.41 (s, 9H, OC(CH_3)$_3$), 1.24 (s, 12H, pinacol CH_3), 1.21 – 1.08 (m, 2H, CH_2), 1.02 – 0.96 (m, 2H, CH_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.6 (*C*=O), 83.8 (pinacol O*C*(R)(CH_3)$_2$), 79.1 (O*C*(CH_3)$_3$), 45.4 (*C*H), 29.1 (CH_2), 28.6 (OC(CH_3)$_3$), 26.7 (2 × CH_2), 24.9 (pinacol CH_3), signals for N(CH_2)$_2$ were not observed. All characterisation data is consistent with that reported previously.[113]

6.3.2. Asymmetric borylation of *tert*-butyl piperidine-1-carboxylate to give *tert*-butyl (*R*)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)piperidine-1-carboxylate, 178



(+)-Sparteine surrogate (250 mg, 1.28 mmol, 1.7 equiv)[A] was added to a flame dried Schlenk flask and dissolved in anhydrous diethyl ether (2.7 mL). The flask was cooled to –78 °C before the dropwise addition of *sec*-butyllithium (in hexane, 1.28 mmol, 1.7 equiv) and, after complete addition, the reaction was stirred at –78 °C for 15 minutes. After this time, a solution of *tert*-butyl piperidine-1-carboxylate (139 mg, 0.75 mmol, 1.0 equiv) in diethyl ether (0.54 mL) was added dropwise and the reaction maintained at –78 °C for a further 6 hours. Then, 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (349 mg, 1.88 mmol, 2.5 equiv) [B] was added dropwise. The reaction mixture was warmed slowly to room temperature and stirred for 16 hours. The reaction was then diluted with diethyl ether (10 mL) and 1M aqueous HCl (20 mL) was added. The layers were separated, and the aqueous phase was extracted with diethyl ether (3 × 15 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude residue was purified by flash column column chromatography (85:15 pentane/ethyl acetate) to yield **178** (268 mg, 89% yield) as a white solid.

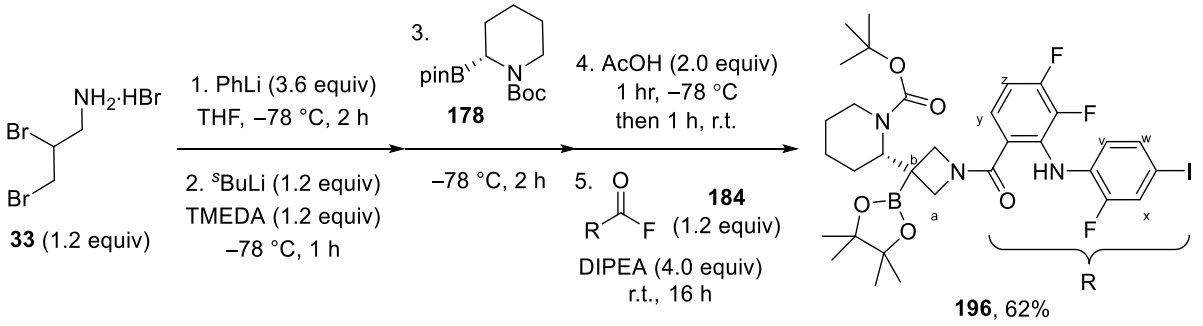
Notes: (A) (+)-Sparteine Surrogate was prepared following a literature procedure[165] and purified by Kugelrohr distillation immediately before use and handled under an inert atmosphere of nitrogen. (B) isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane was distilled prior to use, collecting the second fraction.

R_F 0.18 (80:20 pentane/ethyl acetate); **$[\alpha]_D^{24}$:** +3.0 (88:12 er) (*c* = 8.2, $CHCl_3$); **^{1}H NMR:** (400 MHz, $CDCl_3$) δ 3.68 (br. d, $^2J_{HH}$ = 12.4, 1H, N(Boc)CH_2), 2.67 (td, $^2J_{HH}$ = 12.4, 3.2, 1H, N(Boc)CH_2), 2.28 (dd, $^3J_{HH}$ = 12.3, 3.2, 1H, N(Boc)C*H*(Bpin)), 1.77 (m, 1H, CH_2), 1.54-1.61 (m, 2H, CH_2, CH_2), 1.45 (s, 9H, OC(CH_3)$_3$), 1.43 – 1.17 (m, 3H, CH_2, CH_2, CH_2), 1.13 (s, 12H, OC(CH_3)$_2$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.7 (N*C*(O)OC(CH$_3$)$_3$), 85.7 (O*C*(CH$_3$)$_3$), 79.9 (O*C*(CH$_3$)$_3$), 48.2 (br., N(Boc)*C*H(Bpin)), 42.5 (N(Boc)*C*H$_2$), 28.5 (OC(*C*H$_3$)$_3$), 26.6 (*C*H$_2$),

25.2 (OC(CH_3)$_2$), 24.9 (CH_2), 24.5 (CH_2). NMR spectra consistent with that reported for the racemic synthesis.[114]

6.3.3. Synthesis of cobimetinib

***tert*-Butyl (*S*)-2-(1-(3,4-difluoro-2-((2-fluoro-4-iodophenyl)amino)benzoyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)azetidin-3-yl)piperidine-1-carboxylate, 196**



Phenyllithium (in Bu_2O, 0.87 mmol, 3.6 equiv) was added dropwise (at a rate of 0.02 mL/min) to a suspension of salt **33** (85 mg, 0.29 mmol, 1.2 equiv) in anhydrous THF (0.9 mL) at –78 °C (dry ice/acetone). After complete addition, the resulting solution was stirred for a further 2 hours at –78 °C. TMEDA (40 μL, 0.29 mmol, 1.2 equiv) and *sec*-butyllithium (in hexane, 0.29 mmol, 1.2 equiv) were then added dropwise, and the resulting solution stirred for 1 hour at –78 °C. Boronic ester **178** (75 mg, 0.23 mmol, 1.0 equiv) dissolved in anhydrous THF (0.5 mL) was then added dropwise and the mixture was stirred for 2 h. Acetic acid (30 μL, 0.48 mmol, 2.0 equiv) was then added dropwise and the mixture stirred for 1 h at –78 °C (dry ice/acetone) then warmed to ambient temperature and stirred for a further 1 hour. Diisopropylethylamine (0.17 mL, 0.96 mmol, 4.0 equiv) and acid fluoride **184**[A] (111 mg, 0.28 mmol, 1.2 equiv) were finally added and the resulting mixture was stirred overnight. Et_2O (15 mL) and HCl (1 m aqueous solution, 5 mL) were then added. The mixture was extracted with Et_2O (3× 10 mL) and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (90:10 → 60:40 pentane/ethyl acetate) to yield **196** (109 mg, 62% yield) as a colourless oil.

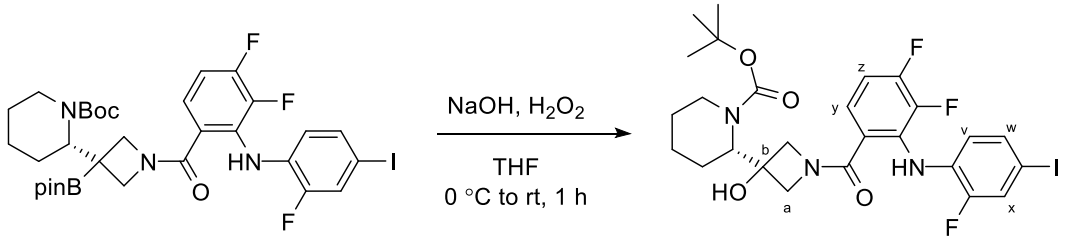
Notes: (A) Acid fluoride **184** was prepared following a literature procedure.[46]

R_F 0.39 (60:40 pentane/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 2975, 2935, 2868, 1634, 1601, 1501, 1444, 1142 and 1045; **HRMS** (ESI): Calcd. for $C_{32}H_{40}BF_3IN_3NaO_5^+$ ([M+Na]$^+$) *m/z* 764.1950, found *m/z* 764.1922; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$**:** –8.2 (88:12 er) (*c* = 2.5, $CHCl_3$);

NMR spectra showed the presence of two rotamers with some peaks resolved and appearing in a 1.85:1 ratio (major/minor)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (br. s, 1H, NH (major)), 8.45 (br. s, NH (minor)), 7.37 (dd, $^{3}J_{HF}$ = 10.3, $^{4}J_{HH}$ = 1.5, 1H, C_xH), 7.31 (br. d, $^{3}J_{HH}$ = 8.5, 1H, C_wH), 7.17 (br. t, J = 6.2, 1H, C_yH (major)), 7.11 (br. t, J = 6.4, C_xH (minor)), 6.78 (m, 1H, C_zH), 6.59 (m, 1H, C_vH), 4.36 (d, $^{2}J_{HH}$ = 8.2, 1H, C_aH) (major)), 4.20 (d, $^{2}J_{HH}$ = 9.8, 1H, C_aH (minor)), 4.16 (d, $^{2}J_{HH}$ = 9.1, 1H, C_aH (minor)), 4.08 (d, $^{2}J_{HH}$ = 10.2, 1H, C_aH (major)), 3.84 (br. m, 2H, C_aH, N(Boc)CH_2), 3.70 (d, $^{2}J_{HH}$ = 10.2, 1H, C_aH), 3.40 (br. s, 1H, N(Boc)CH), 2.91 (br. s, 1H, N(Boc)CH_2), 1.52-1.86 (br. m, 4H, 2 × CH_2), 1.47 – 1.38 (br. m, 2H, CH_2), 1.42 (s, 9H, OC(CH_3)$_3$), 1.17 (s, OC(CH_3)$_2$ (minor)), 1.15 (s, 12H, OC(CH_3)$_2$ (major)); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.8 (NC(O)Ar, (major)), 168.8 (NC(O)Ar, (minor)), 155.9 ((NC(O)OC(CH_3)$_3$), (minor)), 155.8 ((NC(O)OC(CH_3)$_3$), (major)), 153.1 (d, $^{1}J_{CF}$ = 249.5, CF), 152.4 (dd, $^{1}J_{CF}$ = 251.9, 11.6, CF), 143.5 (dd, $^{1}J_{CF}$ = 251.1, J = 14.3, CF), 132.8 (d, $^{4}J_{CF}$ = 2.5, C_w), 132.2 (br. d, J = 7.3, ArC (major)), 132.0 (br. d, J = 7.4, ArC (minor)), 131.1 (d, J = 10.6, ArC), 124.4 (br. m, C_y), 124.1 (d, J = 21.4, C_x), 120.4 (ArC, (minor)), 120.0 (ArC, (major)), 119.5 (C_v), 109.1 (m, C_z), 81.8 (br., OC(CH_3)$_2$), 81.1 (m, CI), 66.1 (br), 61.0 (C_a (major)), 58.2 (br.), 54.9 (C_a (minor)), 54.0 (C_a), 47.4 (br.), 28.4 (OC(CH$_3$)$_3$), 28.1 (br.), 26.7 (CH$_2$), 26.2 (CH$_2$), 25.4 (OC(CH$_3$)$_2$ (minor)), 25.2 (OC(CH$_3$)$_2$ (major)), 24.1 (br., CH$_2$); **^{19}F NMR** (377 MHz, $CDCl_3$) δ –127.0 (t, J = 9.4, CF, (minor)), –127.1 (t, J = 9.4, CF, (major)), –132.4 (br. s, CF), –141.6 (br., CF, (minor)), –141.5 (br. d, J = 14.0, CF, (major)); **^{11}B NMR** ($CDCl_3$, 128 MHz) δ 23.0.

tert-Butyl (*S*)-2-(1-(3,4-difluoro-2-((2-fluoro-4-iodophenyl)amino)benzoyl)-3-hydroxyazetidin-3-yl)piperidine-1-carboxylate, 196'



196 **196'**, 89%

Boronic ester **196** (90 mg, 0.12 mmol, 1.0 equiv) was dissolved in THF (1.3 mL) and cooled to 0 °C (ice/water). A solution of 2 M NaOH/30% $H_2O_{2(aq)}$ (1.5 mL, 2:1 v/v) was then added dropwise to the vigorously stirring reaction mixture, which was subsequently warmed to room temperature and allowed to react for 1 hr. NH_4Cl (saturated aqueous solution, 1 mL) was added

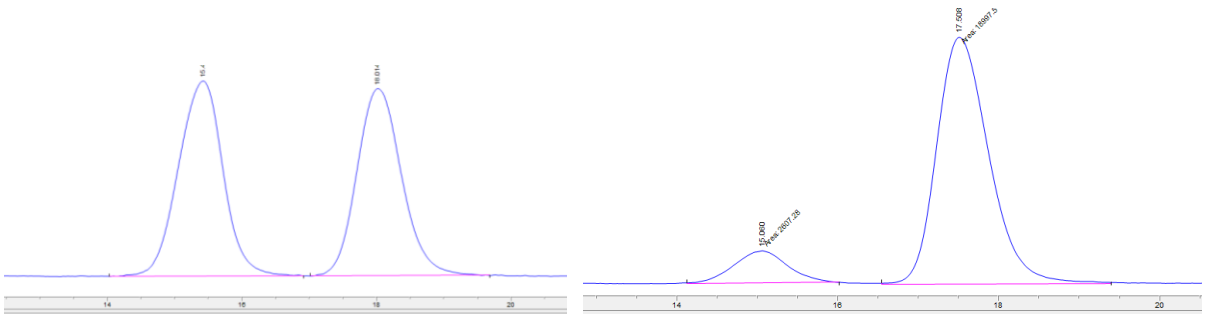
and the reaction mixture was extracted with ethyl acetate (3 × 5 mL). The combined organic fractions were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (90:10 → 50:50 pentane/ethyl actate) to yield alcohol **196'** (68 mg, 89 % yield) as a white foam that solidified under high vacuum.

NMR spectra showed the presence of two rotamers with some peaks resolved and appearing in a 1.22:1 ratio (major/minor)

R_F 0.29 (60:40 pentane/ethyl acetate); **IR** (thin film) ν_{max}: 3315, 2975, 2936, 2871, 1667, 1636, 1602, 1504, 1453, 1159 and 1051 cm^{-1}; **HRMS** (ESI): Calcd for $C_{26}H_{29}N_3O_4F_3INa^+$ ($[M+Na]^+$) *m/z* 654.1044, found *m/z* 654.1047; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$**:** too low to be measurable (88:12 er) (*c* = 4.8, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (br. s, 1H, NH (major)), 8.41 (br. s, NH (minor)), 7.38 (dd, $^3J_{HF}$ = 10.3, $^4J_{HH}$ = 2.0, 1H, C_xH), 7.31 (br. d, $^3J_{HH}$ = 8.5, 1H, C_wH), 7.17 (br., 1H, C_yH), 6.80 (br. app. q, *J* = 8.5, 1H, C_zH), 6.59 (app. td, *J* = 8.6, 5.4, 1H, C_vH), 5.60 (br. s, 1H, O*H*), 4.19 (d, $^2J_{HH}$ = 10.3, 2H, 2 × C_aH (major)), 4.11 (m, 1H, C_aH (minor)), 4.00 (br. m, 2H, 2 × C_aH), 3.86 (br. d, $^2J_{HH}$ = 12.6, 1H, N(Boc)CH_2), 3.38 (br. s, 1H, N(Boc)C*H* (major)), 3.29 (br. s, 1H, N(Boc)C*H* (minor)), 2.90 (br. s, 1H, N(Boc) CH_2), 1.88 (br. s, 1H, CH_2), 1.38 – 1.63 (br. m, 5H, 3 × CH_2), 1.42 (s, 9H, OC(CH_3)$_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.2 (N*C*(O)Ar), 156.0 ((N*C*(O)OC(CH_3)$_3$), (major)), 155.8 ((N*C*(O)OC(CH_3)$_3$), (minor)), 153.3 (d, $^1J_{CF}$ = 250.1, *C*F), 152.8 (dd, $^1J_{CF}$ = 253.2, *J* = 11.5, *C*F), 143.7 (dd, $^1J_{CF}$ = 250.1, *J* = 13.6, *C*F), 133.0 (d, *J* = 2.9, C_w), 132.6 (br., Ar*C* (major)), 132.3 (br., Ar*C* (minor)), 130.9 (d, *J* = 10.2, Ar*C*), 124.3 (d, *J* = 21.4, C_x), 124.3 (br., C_y), 119.9 (br., C_v), 119.7 (Ar*C*, (major)), 119.6 (Ar*C*, (minor)), 109.3 (m, C_z), 81.7 (d, *J* = 7.2, *C*I), 71.2 (br. *C*OH), 81.0 (O*C*(CH_3)$_2$), 65.0 (C_a), 64.8 (br., N(Boc)*C*H), 60.6 (C_a (major)), 60.3 (C_a (minor)), 48.2 (br., N(Boc)*C*H_2), 28.4 (OC(*C*H_3)$_3$), 25.4 (*C*H_2), 25.1 (*C*H_2 (minor)), 24.9 (*C*H_2 (major)), 24.1 (br., *C*H_2); **^{19}F NMR** (377 MHz, $CDCl_3$) δ –127.0 (t, *J* = 9.4, C*F*, (major)), –127.1 (t, *J* = 9.4, C*F*, (minor)), –131.4 (m, C*F*), –141.4 (br. d, *J* = 19.1, C*F*);

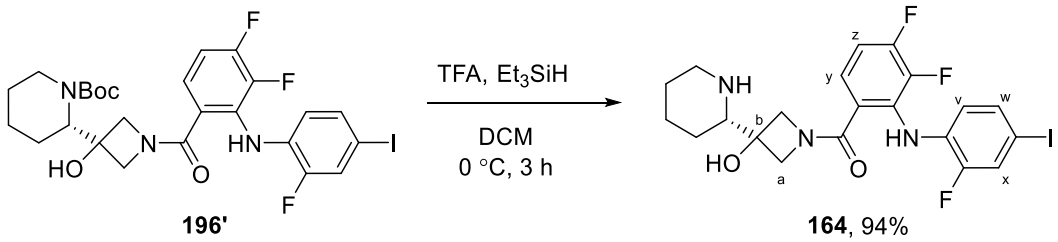
Enantiomeric ratio of 88:12 was determined using chiral HPLC analysis (Chiralpak IB with guard, 3.0% IPA/hexane, 1 mL/min, 25 °C): t_R = t_R = 15.06 [minor, (*R*)], t_R = 17.51 min [major, (*S*)].



Time	Type	Area	Height	Width	Area%
15.419	VV R	6932.2	150.1	0.7169	51.037
18.014	BV R	6650.4	144	0.707	48.963

Time	Type	Area	Height	Width	Area%
15.06	MM	2607.3	55.2	0.7877	12.068
17.508	MM	18997.5	420.6	0.7527	87.932

(*S*)-(3,4-Difluoro-2-((2-fluoro-4-iodophenyl)amino)phenyl)(3-hydroxy-3-(piperidin-2-yl)azetidin-1-yl)methanone (cobimetinib) (164)



196' **164**, 94%

Compound **196'** (60 mg, 0.095 mmol, 1.0 equiv) was dissolved in anhydrous DCM (2.8 mL) and cooled to 0 °C (ice/water). Triethylsilane (90 µL, 0.56 mmol, 5.9 equiv) was added followed by the dropwise addition of trifluoroacetic acid (0.6 mL). The reaction was stirred at 0 °C for 3 hours. After this time, toluene (10 mL) was added and the volatiles removed under reduced pressure. Then, DCM (5 mL) and water (5 mL) were added and, with stirring, a solution of NaOH (2 m aqueous solution, 0.2 mL). The layers were separated, and the aqueous layer extracted with DCM (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give cobimetinib **164** (free base) (50 mg, 94% yield).

M.p. 161.1−161.6 °C (recrystallised by dissolving in 1:1 Et2O/hexane and letting the solvent evaporate slowly). Lit. 171−172 °C [23] (no recrystallization solvent given); **IR** (film) ν_{max}/cm^{-1}: 3297, 3075, 2933, 2855, 1634, 1601, 1503, 1451, 1292, 1123 and 1052; $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{24}}$**:** too low to be measurable (88:12 er) (*c* = 3.4, $CHCl_3$);

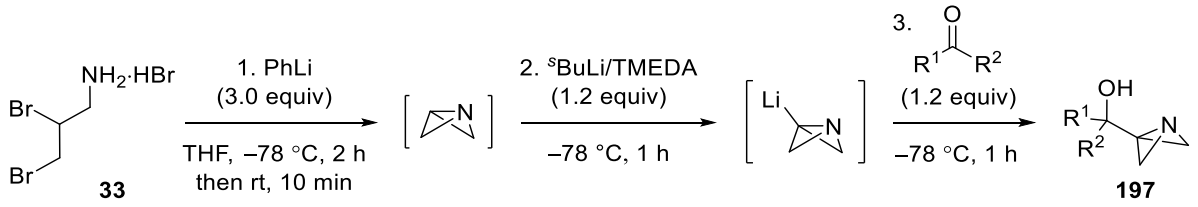
NMR spectra showed the presence of two rotamers with some peaks resolved and appearing in a 1.2:1 ratio (major/minor)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (br., 1H, aniline N*H*), 7.39 (dd, $^3J_{HF}$ = 10.3, $^4J_{HH}$ = 1.9, 1H, C_xH), 7.32 (dt, $^3J_{HH}$ = 8.5, $^4J_{HH}$ = 1.4, 1H, C_wH), 7.11 (m, 1H, C_yH), 6.81 (br. app. q, J = 7.7, 1H, C_zH), 6.59 (app. td, J = 8.6, 5.3, 1H, C_vH), 4.13 (br., 3H, 3 × C_aH), 4.01 (br., 1H, C_aH), 3.13 (br. d, $^2J_{HH}$ = 11.5, 1H, N(Boc)CH_2), 2.73 (br. s, 1H, N(Boc)C*H*), 2.65 (br. s, 1H, N(Boc)CH_2), 2.53 (br. s, 1H, O*H*), 1.78 (br. s, 1H, CH_2), 1.61 (br. m, 2H, 2 × CH_2), 1.39 – 1.16 (m, 4H, 3 × CH_2, piperidine N*H*); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.3 (N*C*(O)Ar), 153.2 (d, $^1J_{HF}$ = 251.0, *C*F), 152.8 (dd, $^1J_{HF}$ = 252.4, $^2J_{HF}$ = 11.9, *C*F), 143.6 (dd, $^1J_{HF}$ = 251.2, 13.4, *C*F), 133.1 (d, J = 3.1, C_w), 132.5 (br., Ar*C*), 130.9 (d, J = 10.7, Ar*C*), 124.5 – 124.2 (m, C_x, C_y), 119.8 (br., C_v), 109.5 (m, C_z), 81.8 (d, J = 6.5, *C*I), 71.7 (*C*OH), 65.1 (C_a (major)), 62.5 (C_a (major)), 61.4 (N(Boc)*C*H), 60.3 (C_a (minor)), 58.0 (C_a (minor)), 46.6 (N(Boc)*C*H_2), 25.8 (br. *C*H_2), 25.0 (*C*H_2), 23.9 (*C*H_2); **^{19}F NMR** (377 MHz, $CDCl_3$) δ –127.1 (m, C*F*), –131.0 (m, C*F*), –141.2 (br. s, C*F*).

^{13}C NMR spectrum consistent with that reported in the literature. The ^{1}H NMR data differs slightly due to being taken in a different solvent.[46]

6.4. Synthetic procedures for chapter 4

6.4.1. General procedure E for the synthesis of azabicyclo[1.1.0]butyl alcohols



In a 100 mL Schlenk flask, Phenyllithium (in Bu_2O, 6.0 mmol, 3.0 equiv) was added dropwise (at a rate of 0.11 mL/min) to a suspension of salt **33**^{A} (590 mg, 2.0 mmol, 1.0 equiv) in anhydrous THF (6.4 mL) at –78 °C (dry ice/acetone). After complete addition, the resulting solution was stirred for a further 2 hours at –78 °C. After this time, the reaction mixture was removed from the cooling bath and warmed to room temperature over 10 minutes with stirring (the reaction mixture should be homogeneous once at room temperature). After cooling back down to –78 °C, TMEDA (0.36 mL, 2.4 mmol, 1.2 equiv) was then added followed by *sec*-butyllithium (in cyclohexane, 2.4 mmol, 1.2 equiv) dropwise (at a rate of 0.11 mL/min), and the resulting solution stirred for 1 hour at –78 °C. After this time, the ketone/aldehyde (0.26 mmol, 1.3 equiv) was added dropwise, either neat or as a solution in anhydrous THF. The reaction was stirred for a further 1 hour at –78 °C. Diethyl ether or ethyl acetate (30 mL)

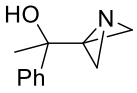
and water (20 mL) were then added, and the reaction mixture transferred to a separating funnel. The phases were separated, and the aqueous phase was extracted with diethyl ether or ethyl acetate (3 × 30 mL) and the combined organic phases were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure.

The crude NMR yield of the product was then determined by quantitative ^{1}H NMR. The crude mixture was dissolved in deuterated chloroform and dibromomethane (42 μL, 0.60 mmol, 0.3 equiv) was added as an internal standard. After the yield was determined by ^{1}H NMR, the crude product was transferred to a volumetric flask, the concentration calculated and the volume corresponding to 0.25 mmol was removed by syringe and transferred to a round bottom flask and evacuated for any further reaction. The crude azabicyclo[1.1.0]butyl carbinols (**197**) can be stored for extended periods (weeks) in a freezer under inert atmosphere without degradation.

Notes: (A) Salt **33** was synthesised according to a reported procedure.[28]

6.4.2. Synthesis of azabicyclo[1.1.0]butyl carbinols

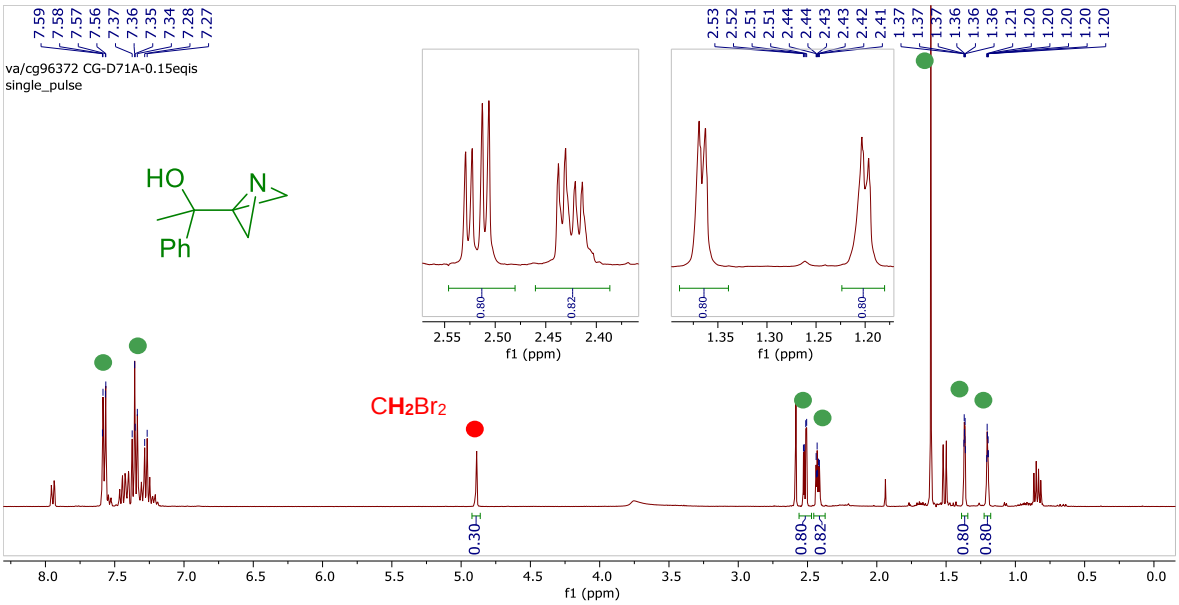
1-(1-Azabicyclo[1.1.0]butan-3-yl)-1-phenylethan-1-ol, 197a



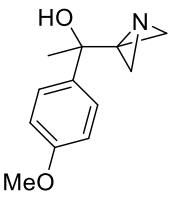
Prepared using general procedure E on a 4.0 mmol scale. Acetophenone (0.60 mL, 5.2 mmol, 1.3 equiv) was added neat to the reaction. ^{1}H NMR yield: 80%.

HRMS (ESI): Calcd. for $C_{11}H_{13}NONa^+$ ($[M+Na]^+$) *m*/*z* 198.0889, found *m*/*z* 198.0889.

Crude ^{1}H NMR ($CDCl_3$, 400 MHz) of **197a**



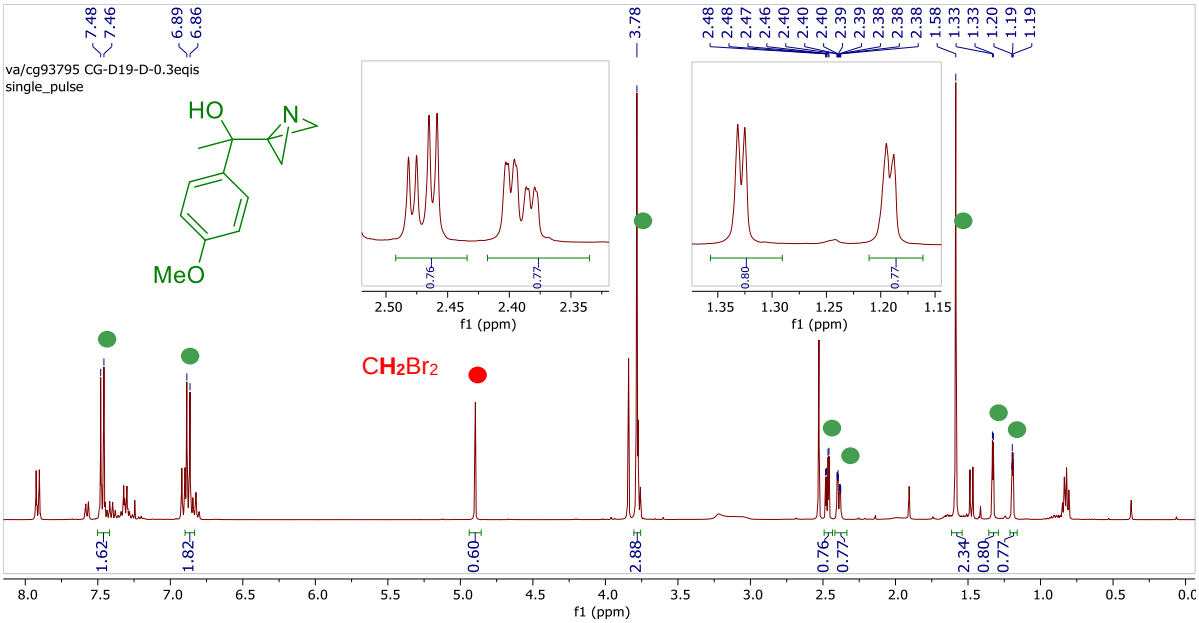
1-(1-Azabicyclo[1.1.0]butan-3-yl)-1-(4-methoxyphenyl)ethan-1-ol, 197b



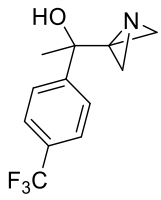
Prepared using general procedure E. 4′-Methoxyacetophenone (0.390 g, 2.6 mmol, 1.3 equiv) was weighed into a vial which was evacuated and backfilled with nitrogen. Anhydrous THF (1.5 mL) was added and this solution was added dropwise to the reaction. ^{1}H NMR yield: 70%.

HRMS (ESI): Calcd. for $C_{12}H_{15}NO_2Na^+$ ([M+Na]$^+$) *m/z* 228.0995, found *m/z* 228.1006.

Crude ^{1}H NMR ($CDCl_3$, 400 MHz) of **197b**



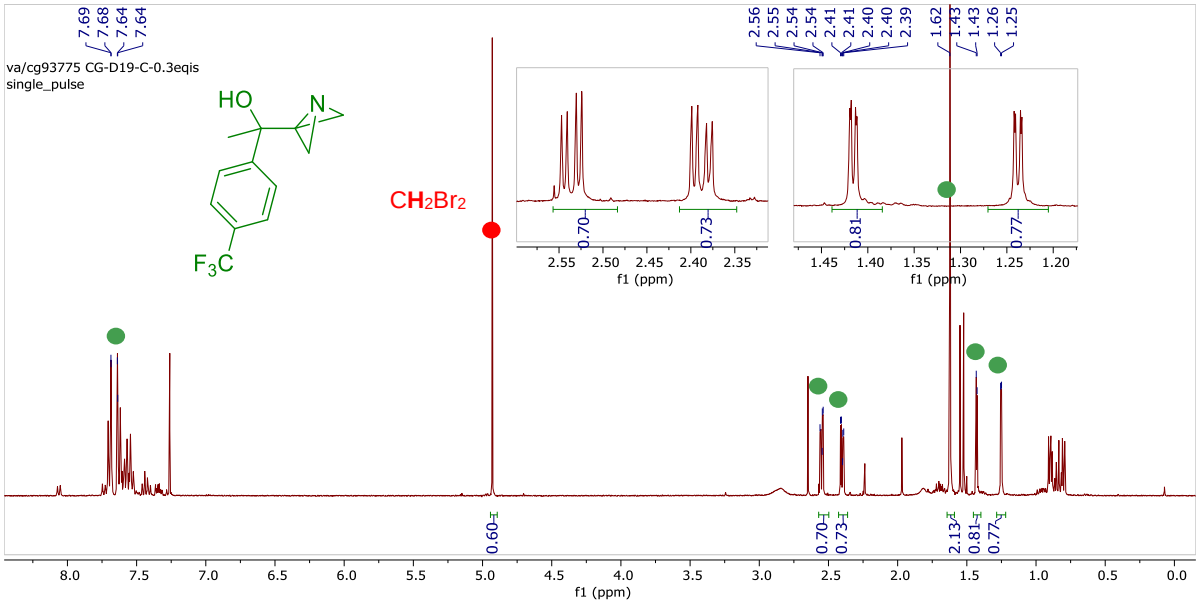
1-(1-Azabicyclo[1.1.0]butan-3-yl)-1-(4-(trifluoromethyl)phenyl)ethan-1-ol, 197c



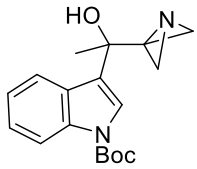
Prepared using general procedure E. 4′-(Trifluoromethyl)acetophenone (0.490 g, 2.6 mmol, 1.3 equiv) was weighed into a vial, which was evacuated and backfilled with nitrogen. Anhydrous THF (1.5 mL) was added, and this solution was added dropwise to the reaction. ^{1}H NMR yield: 70%.

HRMS (ESI): Calcd. for $C_{12}H_{13}F_3NO^+$ ([M+Na]$^+$) *m*/*z* 244.0944, found *m*/*z* 244.0944.

Crude ^{1}H NMR ($CDCl_3$, 400 MHz) of **197c**



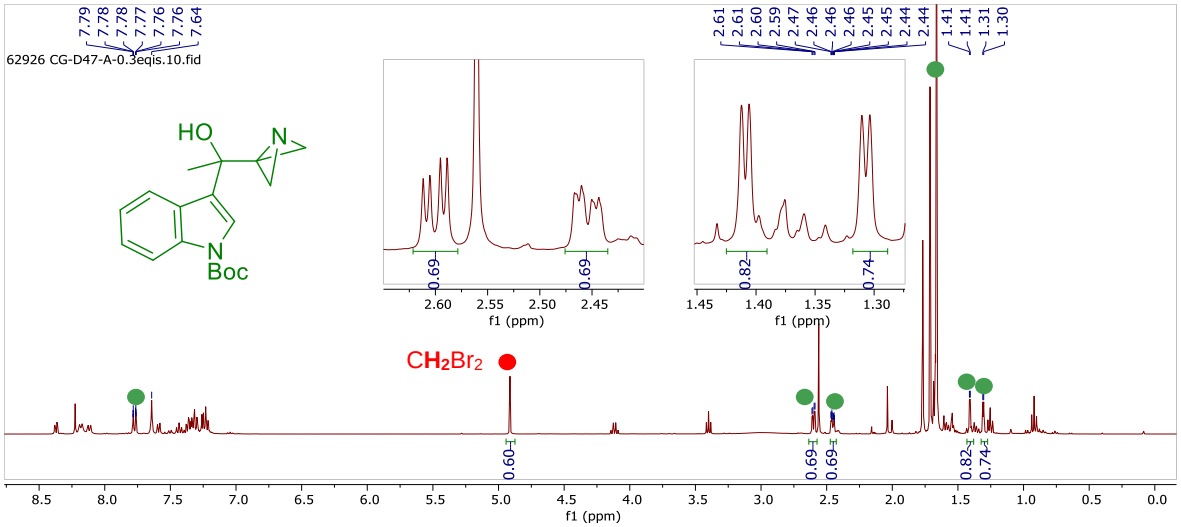
(1- *tert*-Butyl 3-(1-(1-azabicyclo[1.1.0]butan-3-yl)-1-hydroxyethyl)-1H-indole-1-carboxylate, 197d



Prepared using general procedure E. *tert*-Butyl 3-acetyl-1H-indole-1-carboxylate[A] (674 mg, 2.6 mmol, 1.3 equiv) was weighed into a vial which was evacuated and backfilled with nitrogen. Anhydrous THF (5 mL) was added and this solution was added dropwise to the reaction mixture over 3 minutes. ^{1}H NMR yield: 69%.

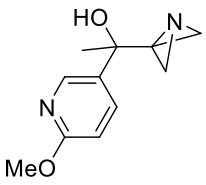
HRMS (ESI): Calcd. for $C_{18}H_{22}N_2O_3Na^+$ ([M+Na]$^+$) *m*/*z* 337.1523, found *m*/*z* 337.1525.

Crude ^{1}H NMR ($CDCl_3$, 400 MHz) of **197d**



Notes: (A) Prepared according to a literature procedure.[166]

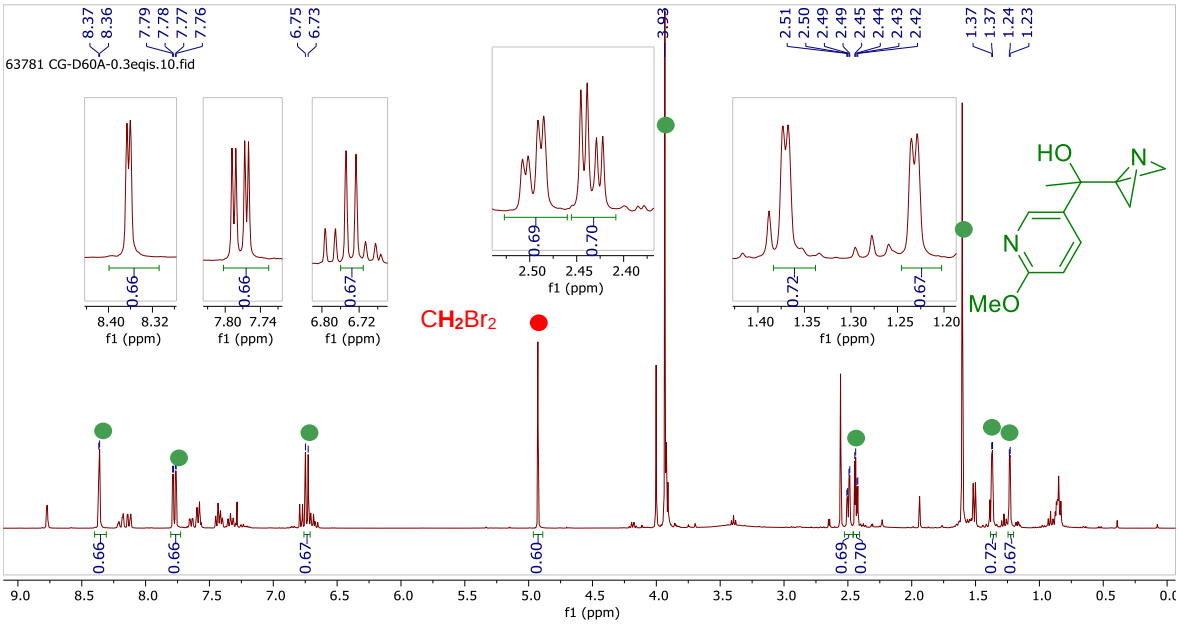
1-(1-Azabicyclo[1.1.0]butan-3-yl)-1-(6-methoxypyridin-3-yl)ethan-1-ol, 197e



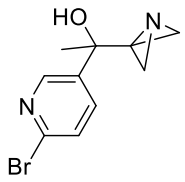
Prepared using general procedure E. 1-(6-methoxypyridin-3-yl)ethan-1-one (393 mg, 2.6 mmol, 1.3 equiv) was weighed into a vial which was evacuated and backfilled with nitrogen. Anhydrous THF (1.5 mL) was added and this solution was added dropwise to the reaction mixture. ^{1}H NMR yield: 66%.

HRMS (ESI): Calcd. for $C_{11}H_{15}N_2O_2^+$ ($[M+H]^+$) *m/z* 207.1128, found *m/z* 207.1132.

Crude ^{1}H NMR ($CDCl_3$, 400 MHz) of **197e**



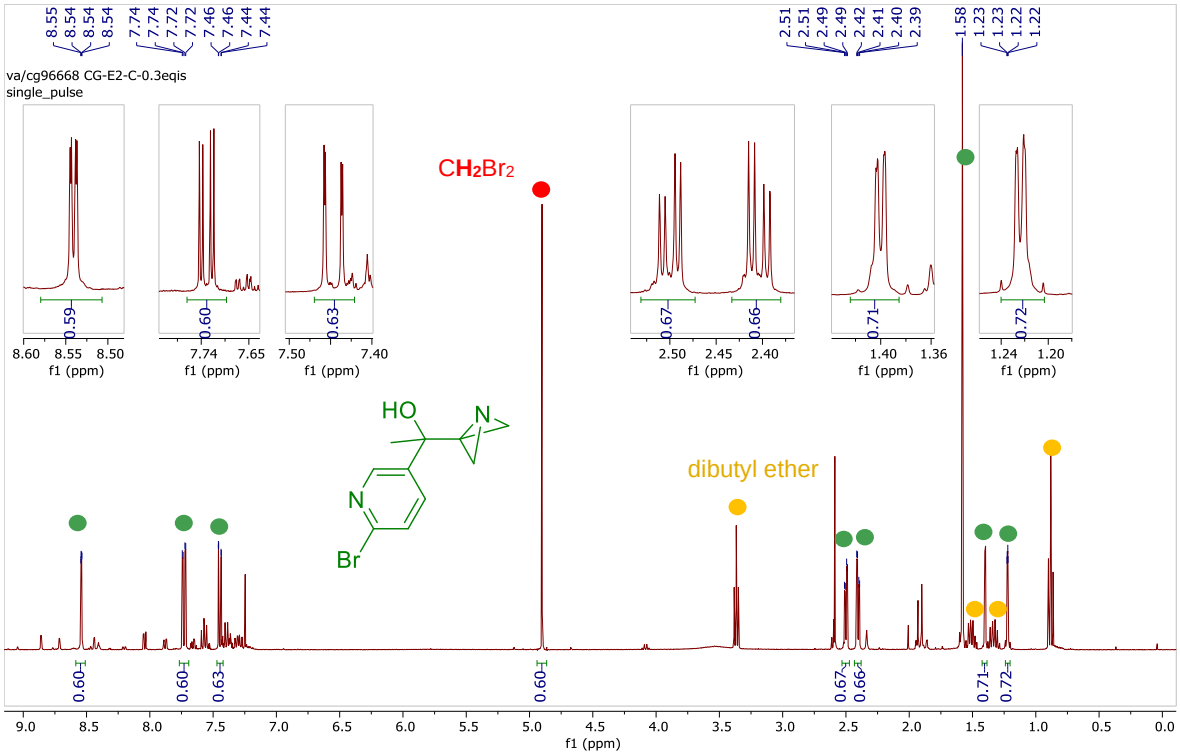
1-(1-Azabicyclo[1.1.0]butan-3-yl)-1-(6-bromopyridin-3-yl)ethan-1-ol, 197f



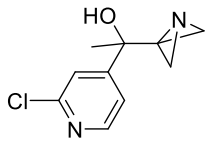
Prepared using general procedure E. 1-(6-Bromopyridin-3-yl)ethan-1-one (520 mg, 2.6 mmol, 1.3 equiv) was weighed into a vial which was evacuated and backfilled with nitrogen. Anhydrous THF (5 mL) was added and this solution was added dropwise to the reaction mixture over 3 minutes. ^{1}H NMR yield: 59%.

HRMS (ESI): Calcd. for $C_{10}H_{11}BrN_2ONa^+$ ([M+Na]$^+$) *m/z* 276.9947, found *m/z* 276.9954.

Crude ^{1}H NMR ($CDCl_3$, 400 MHz) of **197f**



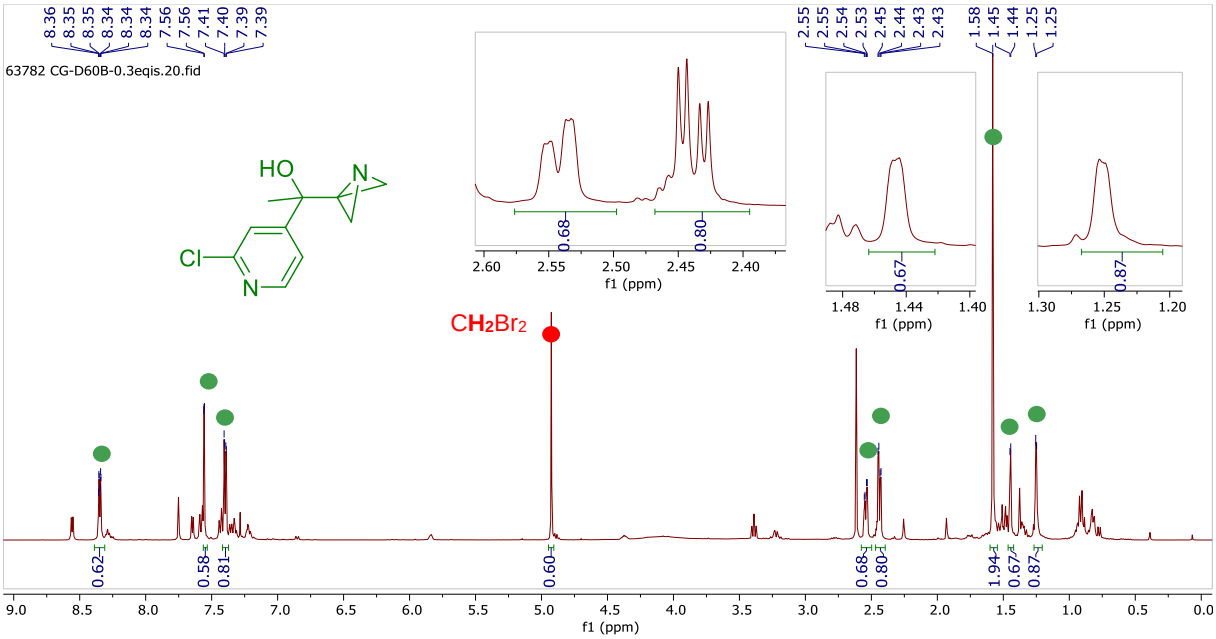
1-(1-Azabicyclo[1.1.0]butan-3-yl)-1-(2-chloropyridin-4-yl)ethan-1-ol, 197g



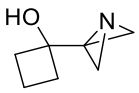
Prepared using general procedure E. 1-(2-Chloropyridin-4-yl)ethan-1-one (405 mg, 2.6 mmol, 1.3 equiv) was weighed into a vial which was evacuated and backfilled with nitrogen. Anhydrous THF (1.5 mL) was added and this solution was added dropwise to the reaction mixture over 3 minutes. ^{1}H NMR yield: 62%.

HRMS (ESI): Calcd. for $C_{10}H_{12}ClN_2O^+$ ([M+H]$^+$) *m/z* 211.0633, found *m/z* 211.0636.

Crude ^{1}H NMR ($CDCl_3$, 400 MHz) of **197g**



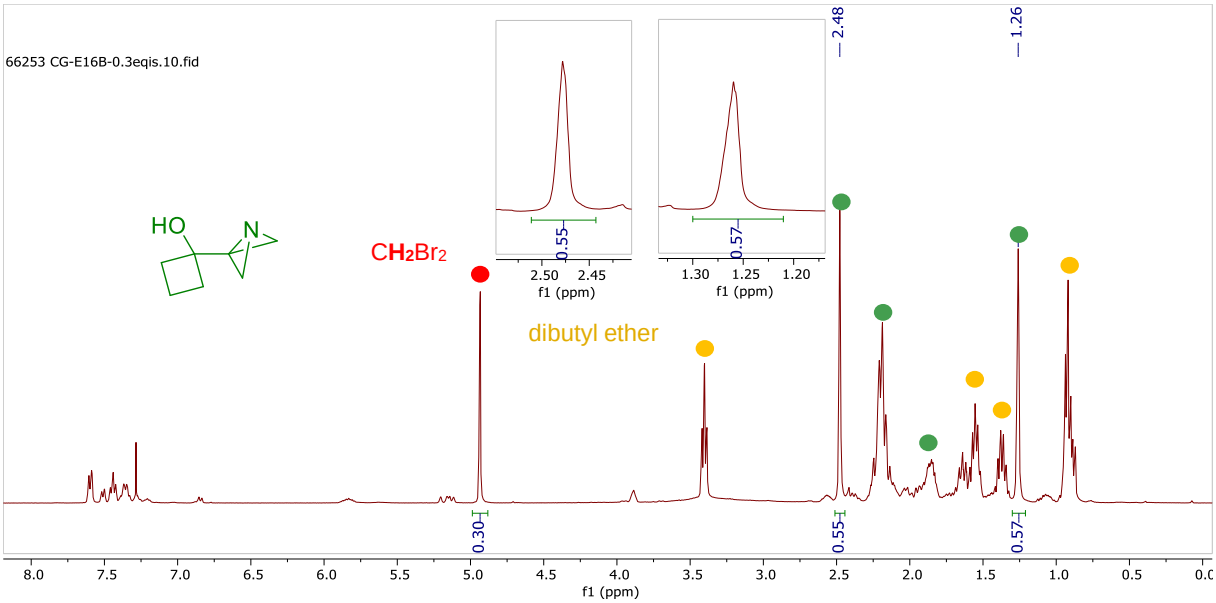
1-(1-Azabicyclo[1.1.0]butan-3-yl)cyclobutan-1-ol, 197h



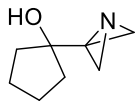
Prepared using general procedure E. Cyclobutanone (0.19 mL, 2.6 mmol, 1.3 equiv) was added neat to the reaction dropwise over 10 minutes. ^{1}H NMR yield: 55%.

HRMS (ESI): Calcd. for $C_7H_{12}NO^+$ ($[M+H]^+$) *m/z* 126.0913, found *m/z* 126.0918.

Crude ^{1}H NMR ($CDCl_3$, 400 MHz) of **197h**



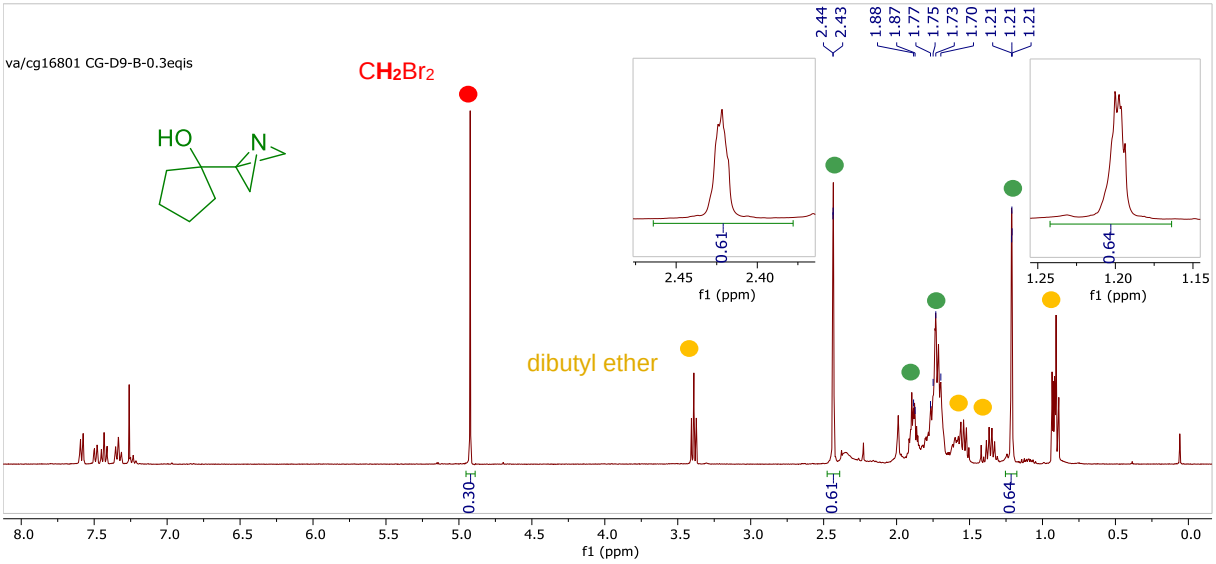
1-(1-Azabicyclo[1.1.0]butan-3-yl)cyclopentan-1-ol, 197i



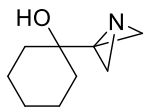
Prepared using general procedure E on a 1.0 mmol scale. Cyclopentanone (0.11 mL, 1.3 mmol, 1.3 equiv) was added neat to the reaction. ^{1}H NMR yield: 61%.

HRMS (APCI): Calcd. for $C_8H_{13}NO^+$ ($[M+Na]^+$) *m/z* 140.1070, found *m/z* 140.1071.

Crude ^{1}H NMR ($CDCl_3$, 400 MHz) of **197i**



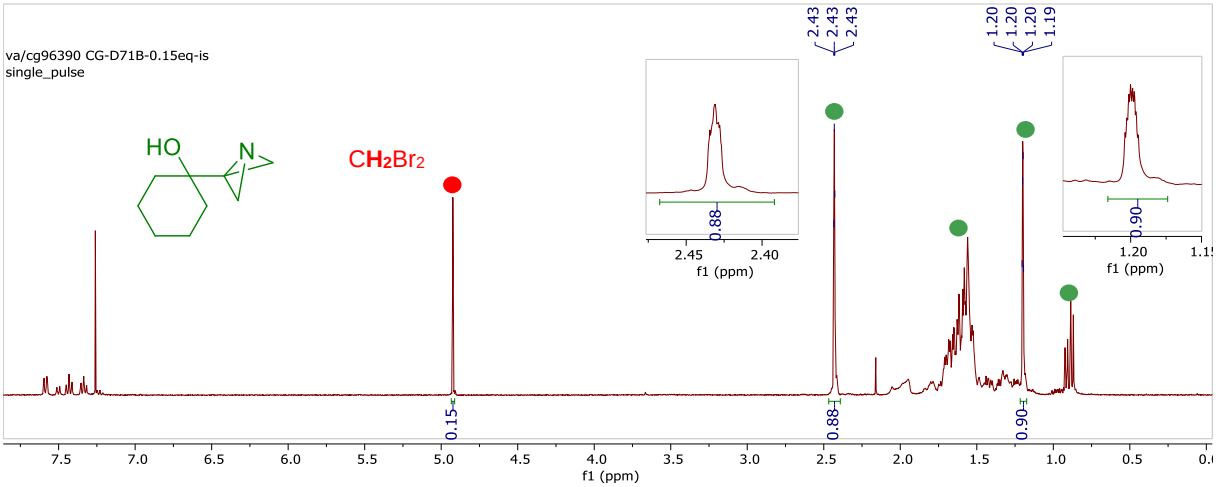
1-(1-Azabicyclo[1.1.0]butan-3-yl)cyclohexan-1-ol, 197j



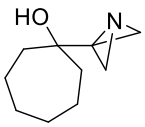
Prepared using general procedure E on a 4.0 mmol scale. Cyclohexanone (0.62 mL, 5.2 mmol, 1.3 equiv) was added neat to the reaction. ^{1}H NMR yield: 88%.

HRMS (ESI): Calcd. for $C_9H_{15}NONa^+$ ($[M+Na]^+$) *m/z* 176.1046, found *m/z* 176.1043.

Crude ^{1}H NMR ($CDCl_3$, 400 MHz) of **197j**



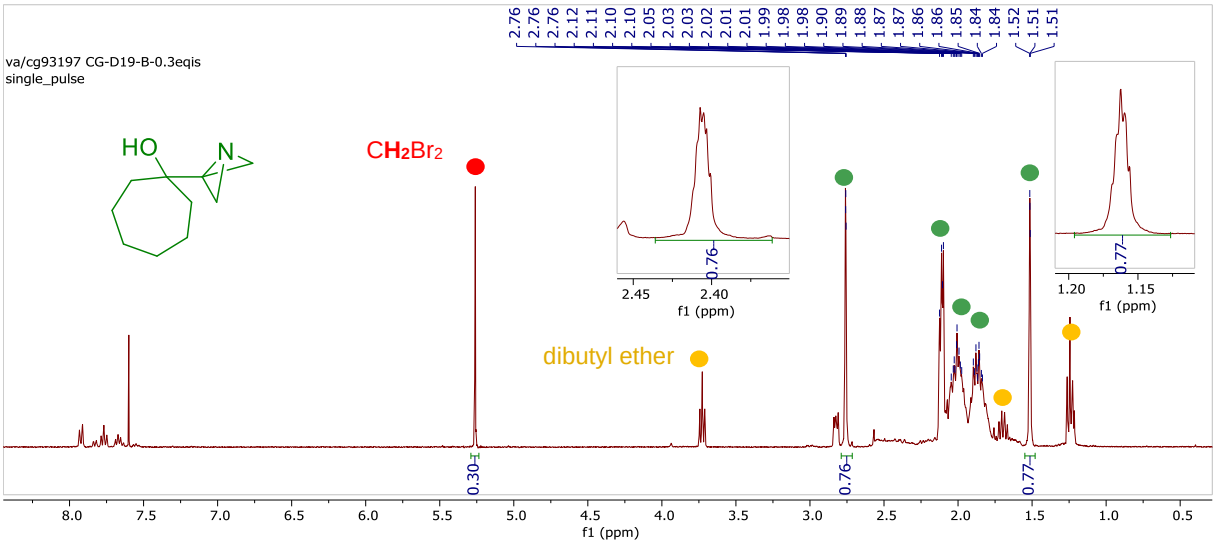
1-(1-Azabicyclo[1.1.0]butan-3-yl)cycloheptan-1-ol, 197k



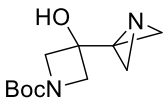
Prepared using general procedure E. Cycloheptanone (0.31 mL, 2.6 mmol, 1.3 equiv) was added neat to the reaction. ^{1}H NMR yield: 75%.

HRMS (APCI): Calcd. for $C_{10}H_{17}NO^+$ ([M+H]$^+$) *m*/*z* 168.1383, found *m*/*z* 168.1385.

Crude ^{1}H NMR ($CDCl_3$, 400 MHz) of **197k**



***tert*-Butyl 3-(1-azabicyclo[1.1.0]butan-3-yl)-3-hydroxyazetidine-1-carboxylate, 197l**

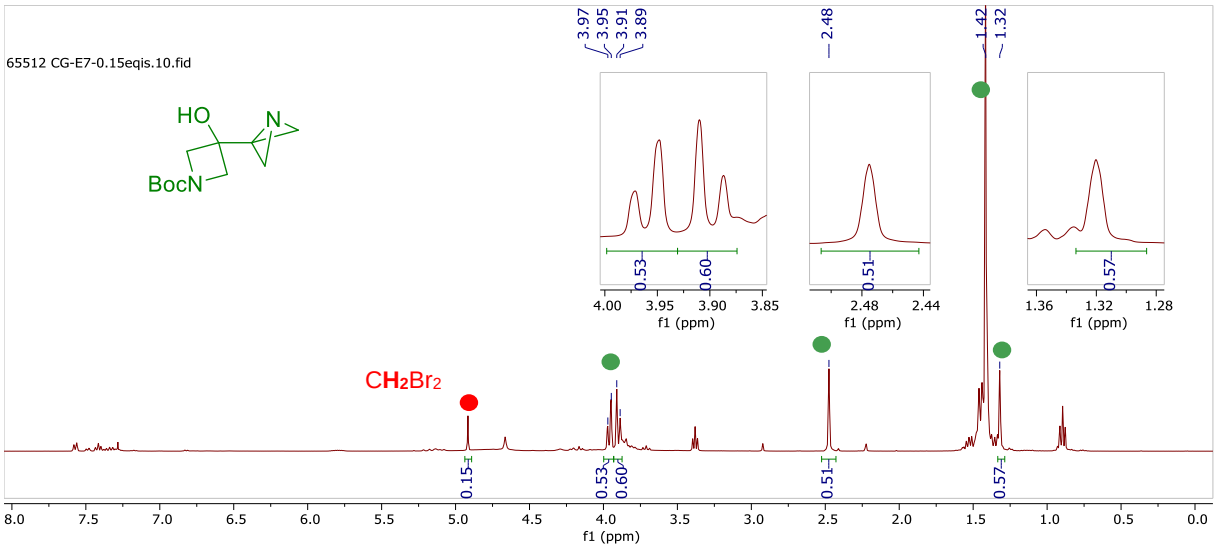


Prepared using general procedure E on a 4 mmol scale. *tert*-Butyl 3-oxoazetidine-1-carboxylate (0.890 g, 5.2 mmol, 1.3 equiv) was weighed into a vial which was evacuated and backfilled with nitrogen. Anhydrous THF

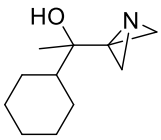
(3.0 mL) was added and this solution was added dropwise to the reaction mixture slowly over 10 minutes. ^{1}H NMR yield: 51%.

HRMS (ESI): Calcd. for $C_{11}H_{18}N_2O_3Na^+$ ([M+Na]$^+$) *m/z* 249.1210, found *m/z* 249.1200.

Crude ^{1}H NMR ($CDCl_3$, 400 MHz) of **197l**



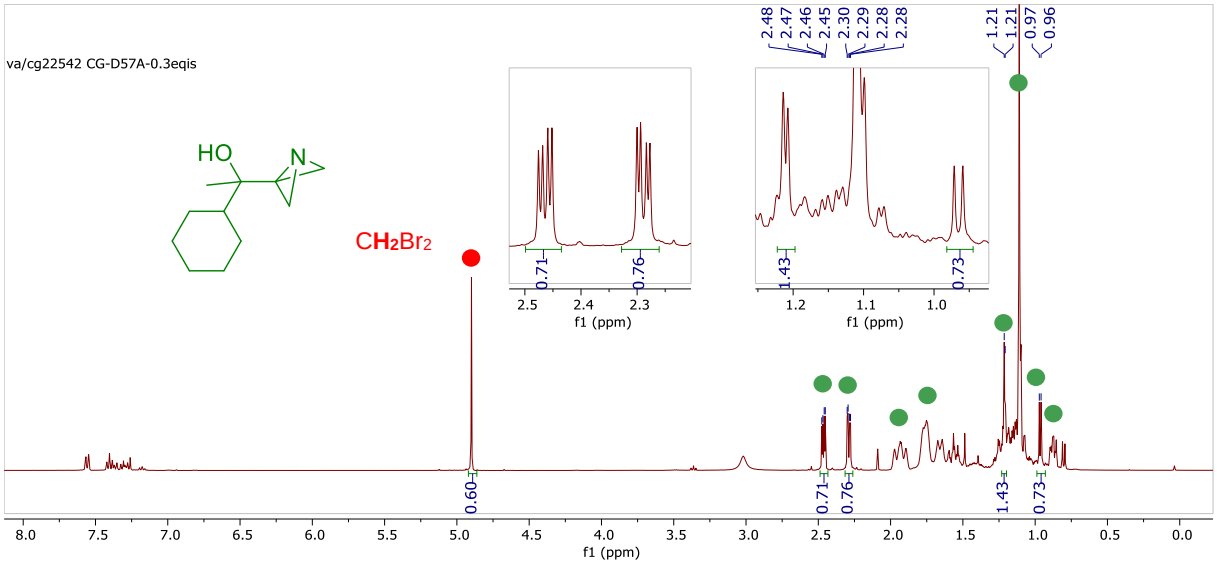
1-(1-Azabicyclo[1.1.0]butan-3-yl)-1-cyclohexylethan-1-ol, 197m



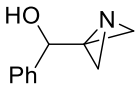
Prepared using general procedure E. 1-Cyclohexylethan-1-one (0.36 mL, 2.6 mmol, 1.3 equiv) was added neat to the reaction. ^{1}H NMR yield: 71%.

HRMS (ESI): Calcd. for $C_{11}H_{19}NONa^+$ ([M+Na]$^+$) *m/z* 204.1359, found *m/z* 204.1353.

Crude ^{1}H NMR ($CDCl_3$, 400 MHz) of **197m**



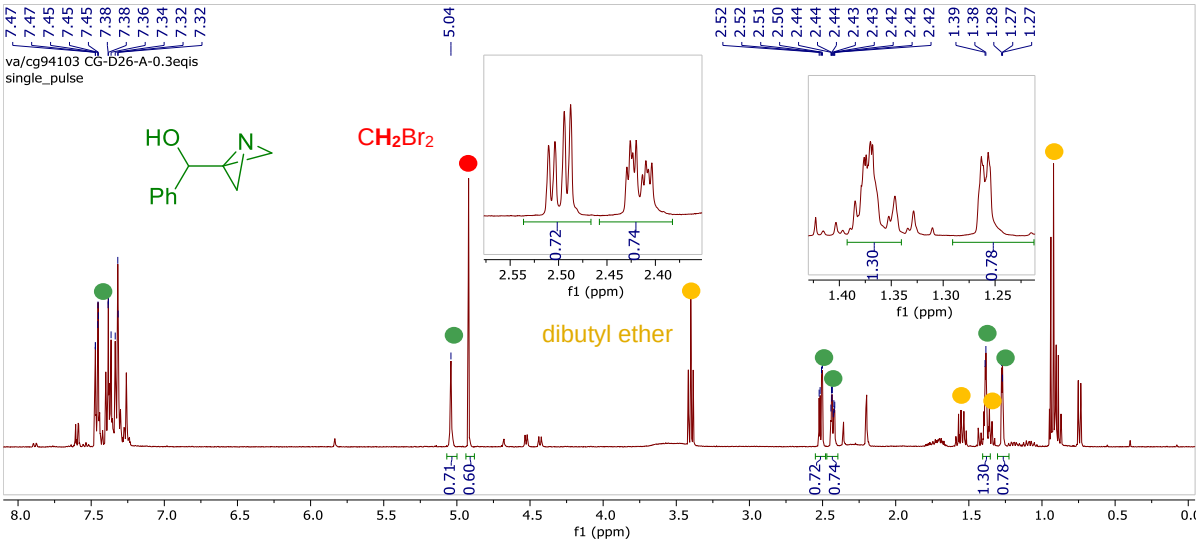
(1-Azabicyclo[1.1.0]butan-3-yl)(phenyl)methanol, 197n



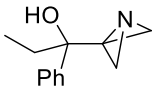
Prepared using general procedure E. Benzaldehyde (0.26 mL, 2.6 mmol, 1.3 equiv) was added neat to the reaction. ^{1}H NMR yield: 71%.

HRMS (ESI): Calcd. for $C_{10}H_{11}NONa^+$ ($[M+Na]^+$) *m/z* 184.0733, found *m/z* 184.0736.

Crude ^{1}H NMR ($CDCl_3$, 400 MHz) of **197n**



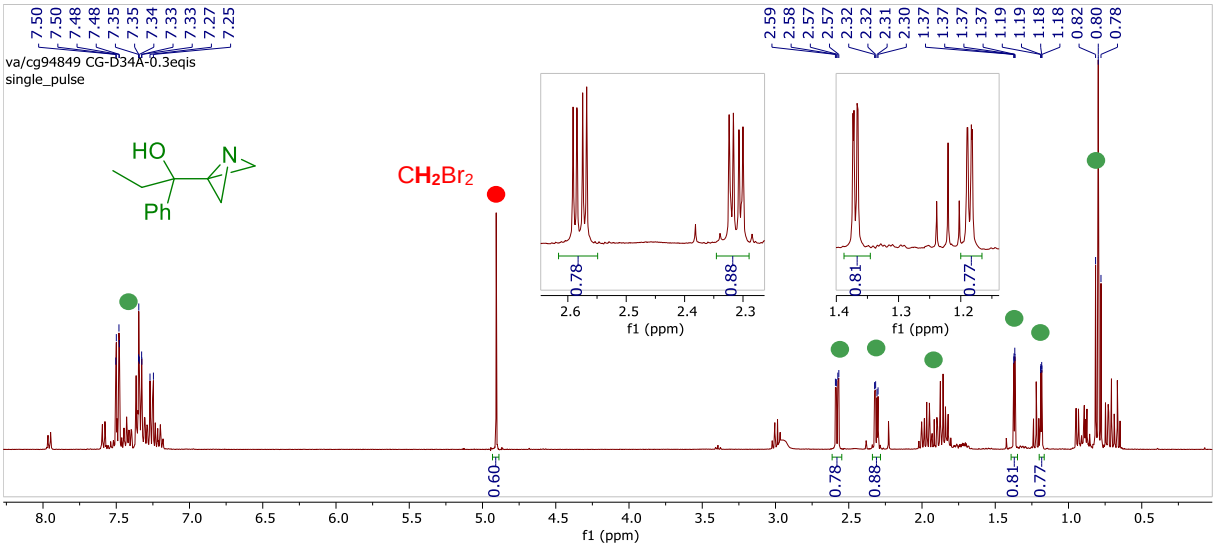
1-(1-Azabicyclo[1.1.0]butan-3-yl)-1-phenylpropan-1-ol, 197o



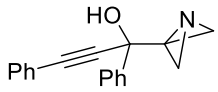
Prepared using general procedure E. Propiophenone (0.30 mL, 2.6 mmol, 1.3 equiv) was added neat to the reaction. ^{1}H NMR yield: 78%.

HRMS (APCI): Calcd. for $C_{12}H_{15}NO^+$ ($[M+H]^+$) *m/z* 190.1226, found *m/z* 190.1227.

Crude ^{1}H NMR ($CDCl_3$, 400 MHz) of **197o**



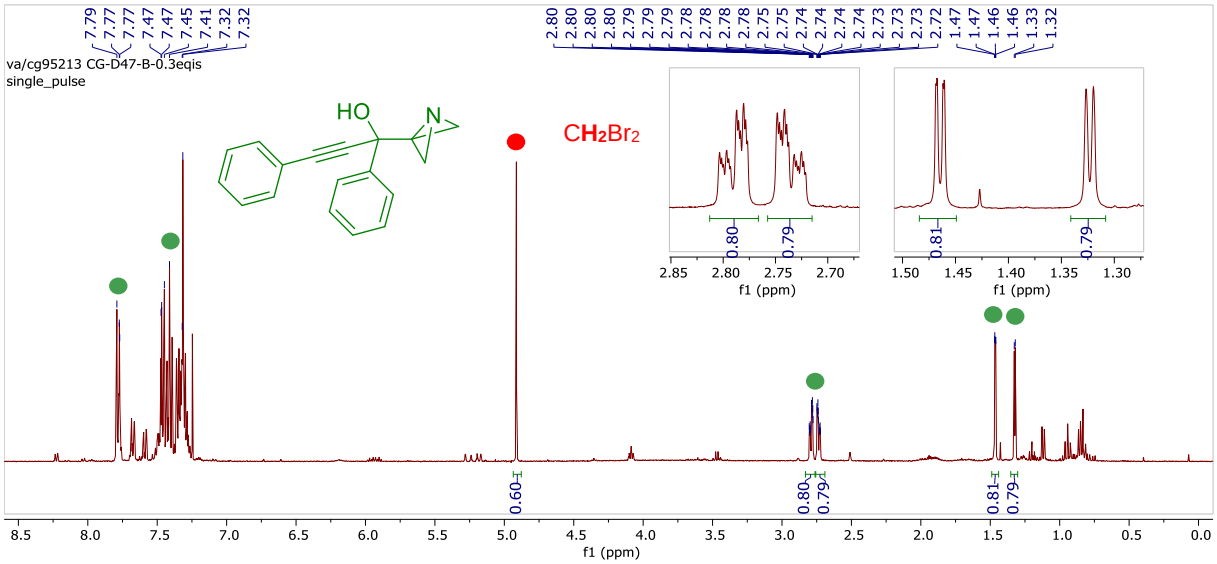
1-(1-Azabicyclo[1.1.0]butan-3-yl)-1,3-diphenylprop-2-yn-1-ol, 197p



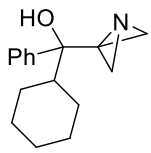
Prepared using general procedure E. 1,3-Diphenylprop-2-yn-1-one (536 mg, 2.6 mmol, 1.3 equiv) was weighed into a vial which was evacuated and backfilled with nitrogen. Anhydrous THF (1.5 mL) was added and this solution was added dropwise to the reaction mixture. ^{1}H NMR yield: 79%.

HRMS (ESI): Calcd. for $C_{18}H_{15}NONa^{+}$ ([M+Na]$^{+}$) *m/z* 284.1046, found *m/z* 284.1043.

Crude ^{1}H NMR ($CDCl_3$, 400 MHz) of **197p**



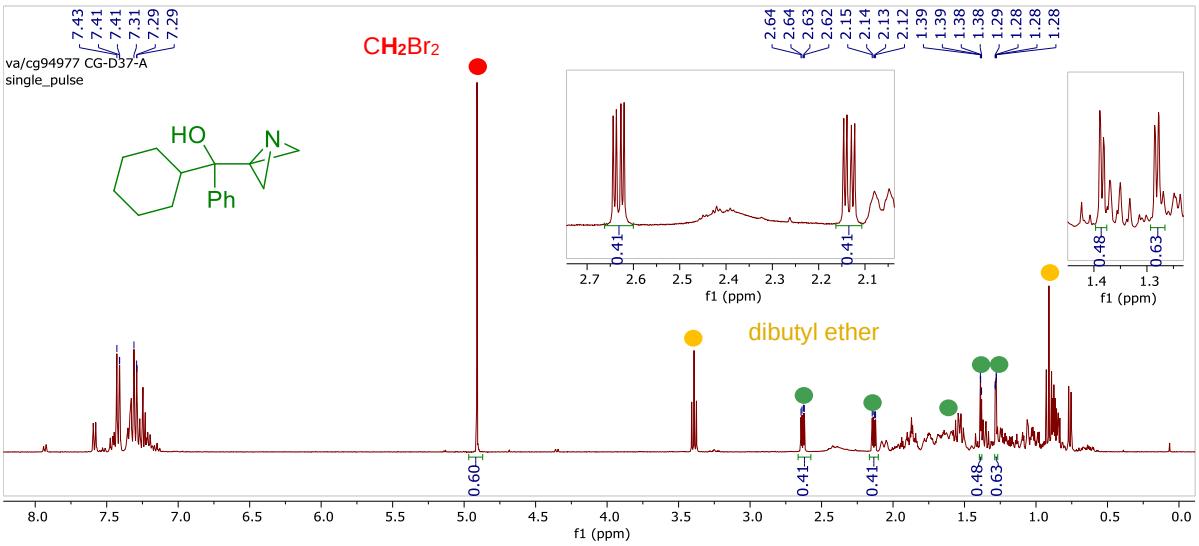
(1-Azabicyclo[1.1.0]butan-3-yl)(cyclohexyl)(phenyl)methanol, 197q



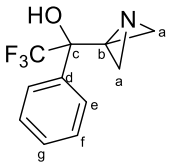
Prepared using general procedure E. Cyclohexyl(phenyl)methanone (308 mg, 2.6 mmol, 1.3 equiv) was weighed into a vial which was evacuated and backfilled with nitrogen. Anhydrous THF (1.5 mL) was added and this solution was added dropwise to the reaction mixture. ^{1}H NMR yield: 40%.

HRMS (APCI): Calcd. for $C_{16}H_{21}NO^{+}$ ([M+Na]$^{+}$) *m/z* 244.1696, found *m/z* 244.1696.

Crude ^{1}H NMR ($CDCl_3$, 400 MHz) of **197q**



1-(1-Azabicyclo[1.1.0]butan-3-yl)-2,2,2-trifluoro-1-phenylethan-1-ol, 197r

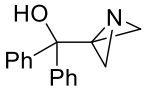


Prepared using general procedure E. 2,2,2-Trifluoro-1-phenylethan-1-one (0.37 mL, 2.6 mmol, 1.3 equiv) was added neat to the reaction. The crude reaction mixture was purified by flash column chromatography (90:10 pentane/ethyl acetate) to give **197r** (231 mg, 50% yield) as a white solid.

R_F 0.46 (80:20 petroleum ether/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 3161, 1453, 1390, 1282, 1247, 1151; **HRMS** (ESI): Calcd. for $C_{11}H_{10}F_3NONa^+$ ($[M+Na]^+$) *m*/*z* 252.0607, found *m*/*z* 252.0612;

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.80 – 7.63 (m, 2H, 2 × C_fH), 7.47 – 7.35 (m, 3H, C_gH, 2 × C_fH), 4.66 (s, 1H, O*H*), 2.91 (ddd, $^{2}J_{HH}$ = 6.7, $^{4}J_{HH}$ = 2.4, 1.2, 1H, C_aH), 2.32 (dd, $^{4}J_{HH}$ = 6.7, 2.5, 1H, C_aH), 1.70 (d, $^{4}J_{HH}$ = 2.4, 1H, C_aH), 1.37 (d, $^{4}J_{HH}$ = 2.5, 1H, C_aH); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 136.1 (C_d), 129.1 (C_g), 128.3 (C_e), 127.3 (C_f), 124.8 (d, $^{1}J_{CF}$ = 286.7, CF_3), 74.4 (q, $^{2}J_{CF}$ = 28.9, C_c), 56.4 (C_a), 52.8 (C_a), 34.4 (C_b); **^{19}F NMR** ($CDCl_3$, 377 MHz) δ –77.43.

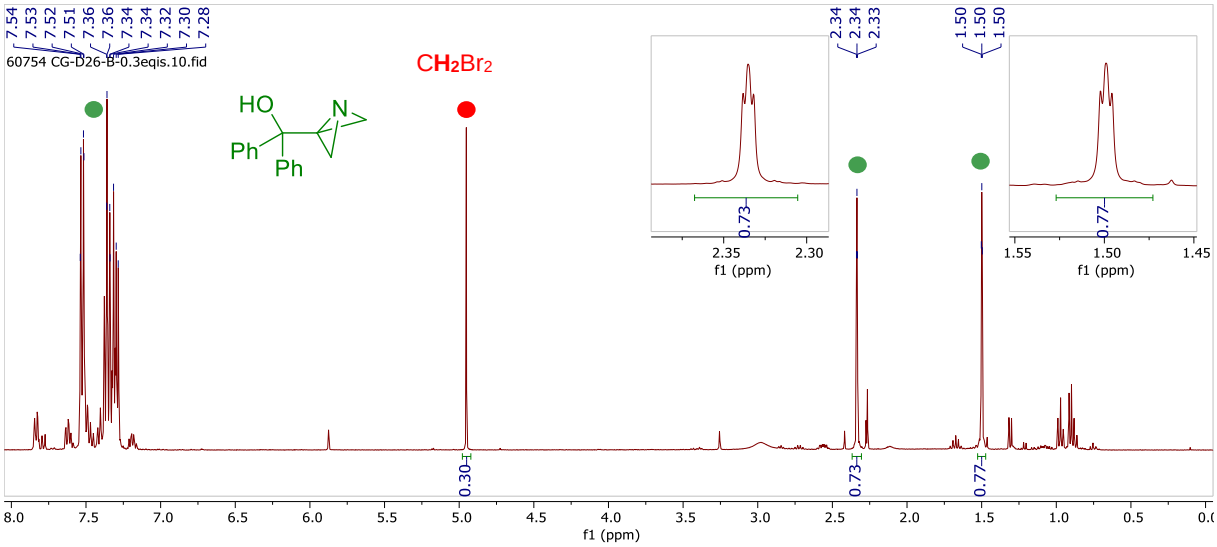
Azabicyclo[1.1.0]butan-3-yl)diphenylmethanol, 197s



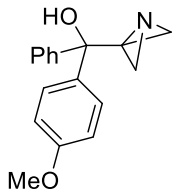
Prepared using general procedure E. Benzophenone (0.474 g, 2.6 mmol, 1.3 equiv) was weighed into a vial which was evacuated and backfilled with nitrogen. Anhydrous THF (1.0 mL) was added, and this solution was added dropwise to the reaction and a further portion of anhydrous THF (0.5 mL) was used to wash the residual reagent from the vial into the reaction mixture. ^{1}H NMR yield: 73%.

HRMS (ESI): Calcd. for $C_{16}H_{15}NONa^+$ ($[M+Na]^+$) *m*/*z* 260.1046, found *m*/*z* 260.1048.

Crude ^{1}H NMR ($CDCl_3$, 400 MHz) of **197s**



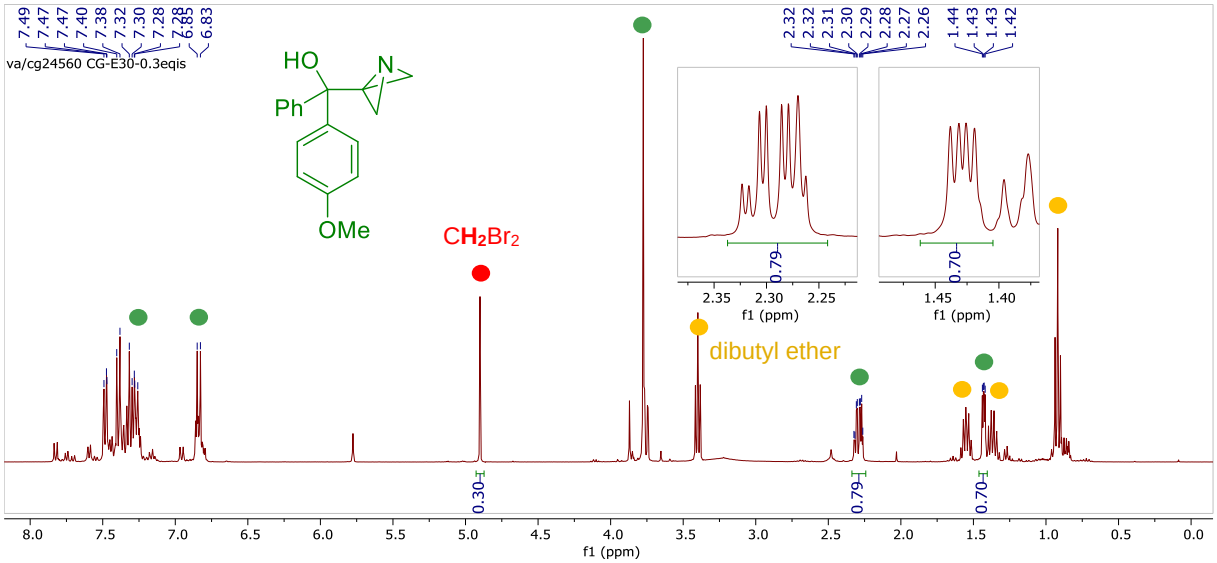
(1-Azabicyclo[1.1.0]butan-3-yl)(4-methoxyphenyl)(phenyl)methanol, 197t



Prepared using general procedure E. 4-Methoxybenzophenone (0.552 g, 2.6 mmol, 1.3 equiv) was weighed into a vial which was evacuated and backfilled with nitrogen. Anhydrous THF (1.0 mL) was added and this solution was added dropwise to the reaction and a further portion of anhydrous THF (0.5 mL) was used to wash the residual reagent from the vial into the reaction mixture. ^{1}H NMR yield: 70%.

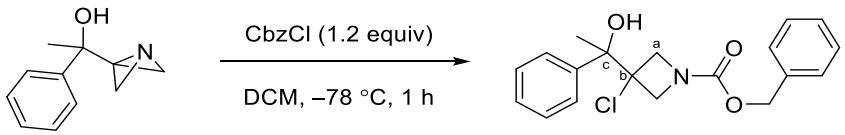
HRMS (ESI): Calcd. for $C_{17}H_{17}NO_2Na^+$ ([M+Na]$^+$) *m/z* 290.1151, found *m/z* 290.1153.

Crude ^{1}H NMR ($CDCl_3$, 400 MHz) of **197t**



6.4.3. Initial reaction investigations

Benzyl 3-chloro-3-(1-hydroxy-1-phenylethyl)azetidine-1-carboxylate, 240



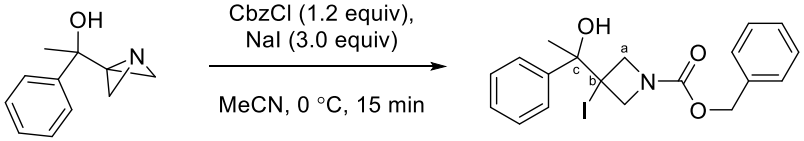
To a round bottom flask containing the 1-(1-azabicyclo[1.1.0]butan-3-yl)-1-phenylethan-1-ol (**197a**, 0.25 mmol, 1.0 equiv) under an inert atmosphere was added anhydrous DCM (2.5 mL). The flask was cooled to –78 °C and benzyl chloroformate (40 μL, 0.30 mmol, 1.2 equiv) was added with stirring. After 1 hour at –78 °C, diethyl ether (10 mL) and saturated aqueous sodium bicarbonate solution (10 mL) were added and the reaction mixture transferred to a separating funnel. The phases were separated, and the aqueous phase was extracted with diethyl ether (3 × 20 mL) and the combined organic phases were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography (95:5 → 80:20 pentane/acetone) to give **240** (64 mg, 74% yield) as a colourless oil.

Reaction repeated on a 0.1 mmol scale in anhydrous acetonitrile and 0 °C for 15 minutes. An NMR yield of 83% was achieved.

R_F 0.32 (80:20 pentane/acetone); **IR** (film) ν_{max}/cm^{-1}: 3400, 2948, 1694, 1446, 1424, 1356, 1213, 1130, 1058, 1033; **HRMS** (ESI): Calcd. for $C_{19}H_{20}ClNO_3Na^+$ ($[M+Na]^+$) *m*/*z* 368.1024, found *m*/*z* 368.1021;

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.57 – 7.49 (m, 2H, ArC*H*), 7.39 – 7.28 (m, 8H, ArC*H*), 5.05 (s, 2H, ROCH_2Ph), 4.69 (dd, $^2J_{HH}$ = 9.8, $^4J_{HH}$ = 1.2, 2H, 2 × C$_a$*H*), 4.19 (d, $^2J_{HH}$ = 9.6, 1H, C$_a$*H*), 3.94 (dd, $^2J_{HH}$ = 9.8, $^4J_{HH}$ = 1.2, 1H, C$_a$*H*), 2.79 (br. s, 1H, O*H*), 1.71 (s, 3H, CH_3); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 156.4 (R_2NC(O)OR), 142.2 (Ar*C*), 136.4 (Ar*C*), 128.6, 128.3 (Ar*C*H), 128.2 (Ar*C*H), 128.1 (Ar*C*H), 128.1 (Ar*C*H), 126.6 (Ar*C*H), 75.8 (C_c), 69.1 (C_b), 67.1 (RO*C*H_2Ph), 61.6 – 60.2 (br., 2 × C_a), 24.5 (*C*H_3).

Benzyl 3-(1-hydroxy-1-phenylethyl)-3-iodoazetidine-1-carboxylate, 242a

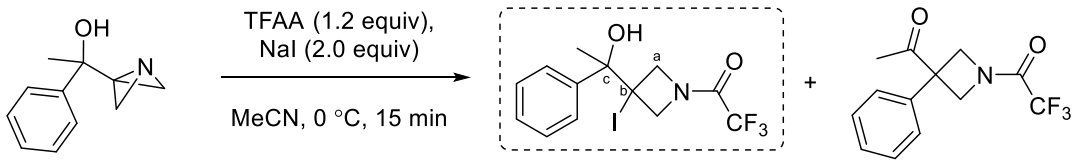


To a round bottom flask containing the 1-(1-azabicyclo[1.1.0]butan-3-yl)-1-phenylethan-1-ol (**197a**, 0.25 mmol, 1.0 equiv) and sodium iodide (75 mg, 2.0 equiv) under an inert atmosphere was added anhydrous acetonitrile (2.5 mL). The flask was cooled to 0 °C and benzyl chloroformate (40 μL, 0.30 mmol, 1.2 equiv) was added with stirring. After 15 minutes at 0 °C, diethyl ether (10 mL) and saturated aqueous sodium bicarbonate solution (5 mL) were added and the reaction mixture transferred to a separating funnel. The phases were separated, and the aqueous phase was extracted with diethyl ether (3 × 20 mL) and the combined organic phases were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography (95:5 → 85:15 pentane/acetone) to give **242a** (100 mg, 91% yield) as a colourless oil.

R_F 0.33 (80:20 pentane/acetone); **IR** (film) ν_{max}/cm^{-1}: 3433, 2969, 1693, 1446, 1422, 1356, 1194, 1129, 1059, 1033; **HRMS** (ESI): Calcd. for $C_{19}H_{20}INO_3Na^+$ ($[M+Na]^+$) *m*/*z* 460.0380, found *m*/*z* 460.0382;

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.49 – 7.43 (m, 2H, ArC*H*), 7.36 – 7.25 (m, 8H, ArC*H*), 5.02 (s, 2H, ROCH_2Ph), 4.97 (d, $^2J_{HH}$ = 10.3, 1H, C_aH), 4.89 (d, $^2J_{HH}$ = 9.9, 1H, C_aH), 4.48 (d, $^2J_{HH}$ = 9.9, 1H, C_aH), 4.31 (dd, $^2J_{HH}$ = 10.3, 1.3, 1H, C_aH), 2.65 (br. s, 1H, O*H*), 1.77 (s, 3H, CH_3); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ (R_2NC(O)OR), 143.6 (br. Ar*C*), 136.4 (Ar*C*), 128.7 (Ar*C*H), 128.3 (Ar*C*H), 128.3 (Ar*C*H), 128.1 (Ar*C*H), 126.6 (Ar*C*H), 76.7 (C_c), 67.2 (RO*C*H_2Ph), 65.0 (br., 2 × C_a), 45.3 (C_b), 26.0 (*C*H_3).

2,2,2-Trifluoro-1-(3-(1-hydroxy-1-phenylethyl)-3-iodoazetidin-1-yl)ethan-1-one, 243



NMR yield: **243**, 40% **241a**, 49%

To a round bottom flask containing the 1-(1-azabicyclo[1.1.0]butan-3-yl)-1-phenylethan-1-ol (**197a**, 0.25 mmol, 1.0 equiv) and sodium iodide (75 mg, 2.0 equiv) under an inert atmosphere was added anhydrous acetonitrile (2.5 mL). The flask was cooled to 0 °C and trifluoroacetic anhydride (40 μL, 0.30 mmol, 1.2 equiv) was added with stirring. After 15 minutes at 0 °C, diethyl ether (10 mL) and saturated aqueous sodium bicarbonate solution (5 mL) were added and the reaction mixture transferred to a separating funnel. The phases were separated, and the aqueous phase was extracted with diethyl ether (3 × 20 mL) and the combined organic phases

were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography (50:50 DCM/pentane → DCM → 98:2 DCM/ethyl acetate). These column conditions were repeated on the mixed fractions. Mixed fractions were observed again and discarded. The combined clean fractions gave **243** (27 mg, 27% yield) as a colourless oil.

R_F 0.39 (95:5 DCM/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 3432, 2970, 2922, 2852, 1684, 1455, 1253, 1206, 1148; **HRMS** (ESI): Calcd. for $C_{13}H_{13}F_3INO_2Na^+$ ($[M+Na]^+$) *m*/*z* 421.9835, found *m*/*z* 421.9832;

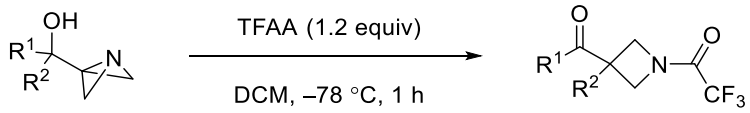
Rotamers observed.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.52 (ddd, $^3J_{HH}$ = 7.8, 6.3, $^4J_{HH}$ = 1.5, 2H, 2 × C_fH), 7.43 – 7.30 (m, 3H, ArCH), 5.35 (d, $^2J_{HH}$ = 11.0, 1H, C_aH), 5.24 (d, $^2J_{HH}$ = 10.7, 1H, C_aH), 5.08 (d, $^2J_{HH}$ = 11.7, 1H, C_aH), 5.01 (d, $^2J_{HH}$ = 11.7, 1H, C_aH), 4.79 (dt, $^2J_{HH}$ = 10.7, $^4J_{HH}$ = 1.5, 1H, C_aH), 4.57 (d, $^2J_{HH}$ = 10.7, 2H, 2 × C_aH), 4.35 (dd, $^2J_{HH}$ = 11.9, $^4J_{HH}$ = 1.8, 1H, C_aH), 2.39 (br. s, 1H, OH), 2.37 (br. s, 1H, OH), 1.85 (s, 3H, CH_3), 1.84 (s, 3H, CH_3); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 156.4 (q, $^2J_{CF}$ = 37.9, CF_3C(O)NR_2), 156.3 (q, $^2J_{CF}$ = 37.9, CF_3C(O)NR_2), 142.6 (C_d), 141.8 (C_d), 128.6 (C_g), 128.5 (C_g), 128.4 (2 × C_e), 128.4 (2 × C_e), 126.7 (2 × C_f), 126.6 (2 × C_f), 116.0 (q, $^1J_{CF}$ = 288.1, CF_3), 116.0 (q, $^1J_{CF}$ = 288.1, CF_3), 76.4 (C_c), 76.4 (C_c), 67.3 (q, $^3J_{CF}$ = 2.38, C_a), 66.4 (q, $^3J_{CF}$ = 2.38, C_a), 64.6 (C_a), 63.7 (C_a), 42.4 (C_b), 26.9 (CH_3), 26.3 (CH_3); **^{19}F NMR** ($CDCl_3$, 377 MHz) δ –72.5, –72.6.

6.4.4. Optimisation of the semipinacol rearrangement reaction

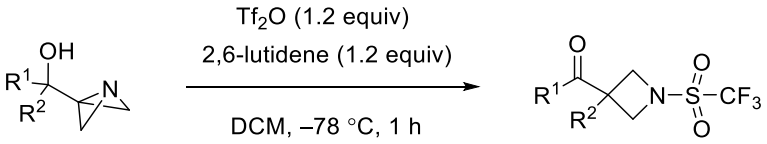
To a round bottom flask containing **197a** (0.10 mmol, 1.0 equiv) under an inert atmosphere was added anhydrous solvent (2.5 mL). The flask was cooled to 0 °C or –78 °C and trifluoroacetic anhydride (16 μL, 0.12 mmol, 1.2 equiv) or trifluoromethanesulfonic anhydride (0.02 mL, 0.12 mmol, 1.2 equiv) was added with stirring. After the reaction time, diethyl ether or ethyl acetate (10 mL) and saturated aqueous sodium bicarbonate solution (10 mL) were added, and the reaction mixture transferred to a separating funnel. The phases were separated, and the aqueous phase was extracted with diethyl ether or ethyl acetate (3 × 20 mL) and the combined organic phases were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. An NMR yield of the product was measured.

6.4.5. General procedure F for the synthesis of keto azetidines



To a round bottom flask containing the azabicyclo[1.1.0]butyl carbinol (0.25 mmol, 1.0 equiv) under an inert atmosphere was added anhydrous DCM (2.5 mL). The flask was cooled to –78 °C and trifluoroacetic anhydride (40 μL, 0.30 mmol, 1.2 equiv) was added with stirring. After 1 hour at –78 °C, diethyl ether or ethyl acetate (10 mL) and saturated aqueous sodium bicarbonate solution (10 mL) were added and the reaction mixture transferred to a separating funnel. The phases were separated, and the aqueous phase was extracted with diethyl ether or ethyl acetate (3 × 20 mL) and the combined organic phases were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure.

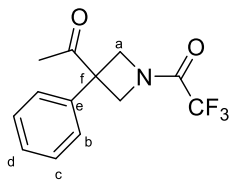
6.4.6. General procedure G for the synthesis of keto azetidines



To a round bottom flask containing the azabicyclo[1.1.0]butyl carbinol (0.25 mmol, 1.0 equiv) under an inert atmosphere was added anhydrous DCM (2.5 mL). The flask was cooled to –78 °C and 2,6-lutidine (34 μL, 0.30 mmol, 1.2 equiv) followed by trifluoromethanesulfonic anhydride (50 μL, 0.30 mmol, 1.2 equiv) was added with stirring. After 1 hour at –78 °C, diethyl ether or ethyl acetate (10 mL) and saturated aqueous sodium bicarbonate solution (10 mL) were added and the reaction mixture transferred to a separating funnel. The phases were separated, and the aqueous phase was extracted with diethyl ether or ethyl acetate (3 × 20 mL) and the combined organic phases were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure.

6.4.7. Scope of the semipinacol rearrangement reaction

1-(3-Acetyl-3-phenylazetidin-1-yl)-2,2,2-trifluoroethan-1-one, 241a

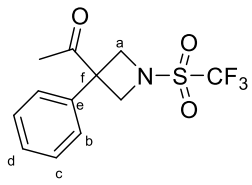


Prepared following general procedure F using the crude 1-(1-azabicyclo[1.1.0]butan-3-yl)-1-phenylethan-1-ol, **197a** (0.25 mmol). The crude reaction mixture was purified by flash column chromatography (95:5 → 75:25 pentane/ethyl acetate) to give **241a** (63 mg, 93% yield) as a white solid.

R_F 0.23 (80:20 petroleum ether/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 2956, 2922, 1695, 1468, 1221, 1205, 1150; **HRMS** (ESI): Calcd. for $C_{13}H_{13}F_3NO_2^+$ ([M+H]$^+$) *m*/*z* 272.0893, found *m*/*z* 272.0891;

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.56 – 7.41 (m, 2H, C_cH), 7.41 – 7.34 (m, 1H, C_dH), 7.24 – 7.18 (m, 2H, C_bH), 5.10 (dt, $^2J_{HH}$ = 9.5, $^4J_{HH}$ = 1.3, 1H, C_aH), 4.66 (d, $^2J_{HH}$ = 10.5, 1H, C_aH), 4.61 – 4.51 (m, 2H, C_aH), 2.05 (s, 3H, CH_3); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 203.7 ($CH_3C(O)C_f$), 156.4 (q, $^2J_{CF}$ = 38.5, $CF_3C(O)NR_2$), 137.8 (C_e), 129.6 (2 × C_c), 128.6 (C_d), 126.2 (2 × C_b), 116.1 (q, $^1J_{CF}$ = 288.2, CF_3), 58.8 (q, $^4J_{CF}$ = 2.5, C_a), 55.7 (C_a), 54.4 (C_f), 24.7 (CH_3); **^{19}F NMR** ($CDCl_3$, 377 MHz) δ –72.54.

1-(3-Phenyl-1-((trifluoromethyl)sulfonyl)azetidin-3-yl)ethan-1-one, 244a

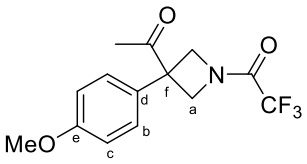


Prepared following general procedure G using the crude 1-(1-azabicyclo[1.1.0]butan-3-yl)-1-phenylethan-1-ol, **197a** (0.25 mmol). The crude reaction mixture was purified by flash column chromatography (98:2 → 80:20 pentane/ethyl acetate) to give **244a** (60 mg, 79% yield) as a white solid.

R_F 0.39 (80:20 petroleum ether/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 2965, 2918, 1714, 1383, 1225, 1193; **HRMS** (ESI): Calcd. for $C_{12}H_{12}F_3NO_3SNa^+$ ([M+Na]$^+$) *m*/*z* 330.0382, found *m*/*z* 330.0376;

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.49 – 7.41 (m, 2H, C_cH), 7.41 – 7.35 (m, 1H, C_dH), 7.20 – 7.12 (m, 2H, C_bH), 4.80 (d, $^2J_{HH}$ = 7.9, 2H, 2 × C_aH), 4.53 (d, $^2J_{HH}$ = 7.9, 2H, 2 × C_aH), 2.05 (CH_3). **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 203.0 ($CH_3C(O)C_f$), 137.3 (C_e), 129.7 (2 × C_c), 128.7 (C_d), 126.0 (2 × C_b), 119.9 (q, $^1J_{CF}$ = 322.3, CF_3), 58.8 (2 × C_a), 53.3 (C_f), 24.6 (CH_3); **^{19}F NMR** ($CDCl_3$, 377 MHz) δ –75.28.

1-(3-Acetyl-3-(4-methoxyphenyl)azetidin-1-yl)-2,2,2-trifluoroethan-1-one, 241b

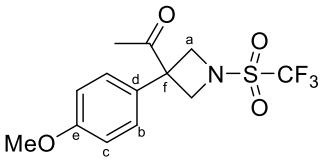


Prepared following general procedure F using the crude 1-(1-azabicyclo[1.1.0]butan-3-yl)-1-(4-methoxyphenyl)ethan-1-ol, **197b** (0.25 mmol). The crude reaction mixture was purified by flash column chromatography (95:5 → 65:35 pentane/ethyl acetate) to give **241b** (66 mg, 88% yield) as an off-white solid.

R_F 0.38 (70:30 petroleum ether/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 2981, 2870, 1698, 1514, 1251, 1145; **HRMS** (ESI): Calcd. for $C_{14}H_{15}F_3NO_3^+$ ($[M+H]^+$) *m*/*z* 302.0999, found *m*/*z* 302.1000;

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.12 (m, 2H, 2 × C_bH), 6.95 (m, 2H, 2 × C_cH), 5.07 (d, $^2J_{HH}$ = 9.5, 1H, C_aH), 4.63 (d, $^2J_{HH}$ = 10.6, 1H, C_aH), 4.53 (d, $^2J_{HH}$ = 9.5, 1H, C_aH), 4.49 (d, $^2J_{HH}$ = 10.6, 1H, C_aH), 3.82 (s, 3H, OCH_3), 2.04 (s, 3H, $C(O)CH_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 204.0 ($CH_3C(O)C_f$), 159.7 (C_e), 156.4 (q, $^2J_{CF}$ = 37.7), 129.6 (C_d), 127.4 (2 × C_b), 116.0 (q, $^1J_{CF}$ = 285.86, CF_3), 115.0 (2 × C_c), 58.8 (q, $^4J_{CF}$ = 2.4, C_a), 55.7 (C_a), 55.5 (OCH_3), 53.7 (C_f), 24.5 ($C(O)CH_3$); **^{19}F NMR** ($CDCl_3$, 377 MHz) δ –72.6.

1-(3-(4-Methoxyphenyl)-1-((trifluoromethyl)sulfonyl)azetidin-3-yl)ethan-1-one, 244b

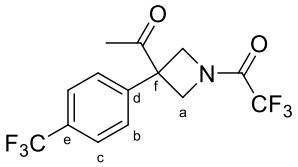


Prepared following general procedure G using the crude 1-(1-azabicyclo[1.1.0]butan-3-yl)-1-(4-methoxyphenyl)ethan-1-ol, **197b** (0.25 mmol). The crude reaction mixture was purified by flash column chromatography (95:5 → 65:35 pentane/ethyl acetate) to give **244b** (60 mg, 71% yield) as a white solid.

R_F 0.51 (70:30 petroleum ether/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 2982, 1869, 1707, 1514, 1384, 1375, 1224, 1190; **HRMS** (ESI): Calcd. for $C_{13}H_{14}F_3NO_4SNa^+$ ($[M+Na]^+$) *m*/*z* 360.0488, found *m*/*z* 360.0489;

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.08 (m, 2H, 2 × C_bH), 6.94 (m, 2H, 2 × C_cH), 4.76 (d, $^2J_{HH}$ = 8.1, 2H, 2 × C_aH), 4.46 (d, $^2J_{HH}$ = 8.1, 2H, 2 × C_aH), 3.80 (s, 3H, OCH_3), 2.02 (s, 3H, $C(O)CH_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 203.3 ($CH_3C(O)C_f$), 159.8 (C_e), 129.1 (C_d), 127.3 (2 × C_b), 119.9 (q, $^1J_{CF}$ = 322.4), 115.0 (2 × C_c), 58.8 (C_a), 55.5 (OCH_3), 52.6 (C_f), 24.4 ($C(O)CH_3$); **^{19}F NMR** ($CDCl_3$, 377 MHz) δ –75.13.

1-(3-Acetyl-3-(4-(trifluoromethyl)phenyl)azetidin-1-yl)-2,2,2-trifluoroethan-1-one, 241c

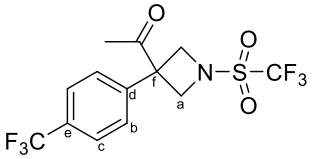


Prepared following general procedure F using the crude 1-(1-azabicyclo[1.1.0]butan-3-yl)-1-(4-(trifluoromethyl)phenyl)ethan-1-ol, **197c** (0.25 mmol). The crude reaction mixture was purified by flash column chromatography (95:5 → 70:30 pentane/ethyl acetate) to give **241c** (74 mg, 87% yield) as a white solid.

R_F 0.25 (70:30 petroleum ether/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 2981, 2870, 1705, 1332, 1146, 1130; **HRMS** (ESI): Calcd. for $C_{14}H_{11}F_6NO_2Na^+$ ($[M+Na]^+$) *m*/*z* 362.0586, found *m*/*z* 362.0582;

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.71 (d, $^3J_{HH}$ = 8.2, 2H, 2 × C_cH), 7.36 (d, $^3J_{HH}$ = 8.2, 2H, 2 × C_bH), 5.12 (d, $^2J_{HH}$ = 9.6, 1H, C_aH), 4.69 (d, $^2J_{HH}$ = 10.7, 1H, C_aH), 4.58 (d, $^2J_{HH}$ = 9.6, 1H, C_aH), 4.54 (d, $^2J_{HH}$ = 10.7, 1H, C_aH), 2.07 (s, 1H, CH_3); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 202.7 (CH_3C(O)C_f), 156.4 (q, $^2J_{CF}$ = 37.9, CF_3C(O)NR_2), 141.7 (C_d), 131.0 (q, $^2J_{CF}$ = 33.1, C_e), 126.8 (2 × C_b), 126.7 (q, $^3J_{CF}$ = 3.7, 2 × C_c), 123.8 (q, $^1J_{CF}$ = 272.4, ArCF_3), 116.0 (q, $^1J_{CF}$ = 288.1, C(O)CF_3), 58.8 (q, $^4J_{CF}$ = 2.4, C_a), 55.7 (C_a), 54.4 (C_f), 24.8 (CH_3); **^{19}F NMR** ($CDCl_3$, 377 MHz) δ -62.89, –72.72.

1-(3-(4-(Trifluoromethyl)phenyl)-1-((trifluoromethyl)sulfonyl)azetidin-3-yl)ethan-1-one, 244c



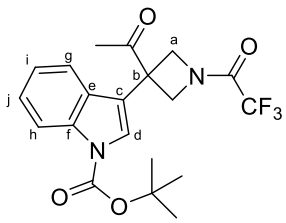
Prepared following general procedure G using the crude 1-(1-azabicyclo[1.1.0]butan-3-yl)-1-(4-(trifluoromethyl)phenyl)ethan-1-ol, **197c** (0.25 mmol). The crude reaction mixture was purified by flash column chromatography (95:5 → 70:30 pentane/ethyl acetate) to give **244c** (56 mg, 60% yield) as a white solid.

R_F 0.20 (70:30 petroleum ether/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 2981, 2870, 1711, 1377, 1332, 1200, 1161, 1120; **HRMS** (ESI): Calcd. for $C_{13}H_{11}F_6NO_3SNa^+$ ($[M+Na]^+$) *m*/*z* 398.0256, found *m*/*z* 398.0256;

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.73 (d, $^3J_{HH}$ = 8.2, 2H, 2 × C_cH), 7.33 (d, $^3J_{HH}$ = 8.2, 2H, 2 × C_bH), 4.83 (d, $^2J_{HH}$ = 8.1, 1H, 2 × C_aH), 4.53 (d, $^2J_{HH}$ = 8.1, 2H, 2 × C_aH), 2.08 (s, 3H, CH_3); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 202.0 (CH_3C(O)C_f), 141.2 (C_d), 131.2 (q, $^2J_{CF}$ = 33.0, C_e), 126.8 (q, $^3J_{CF}$ = 3.7, 2 × C_c), 126.6 (2 × C_b), 123.7 (q, $^1J_{CF}$ = 272.4, ArCF_3), 119.8 (q,

$^1J_{CF}$ = 322.1, SO_2CF_3), 58.7 (C_a), 53.3 (C_f), 24.8 (CH_3); **^{19}F NMR** ($CDCl_3$, 377 MHz) δ –62.89, –75.33.

***tert*-Butyl 3-(3-acetyl-1-(2,2,2-trifluoroacetyl)azetidin-3-yl)-1H-indole-1-carboxylate, 241d**

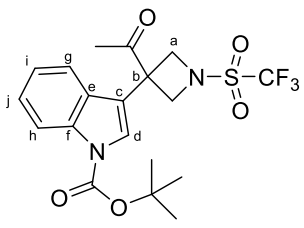


Prepared following general procedure F using the crude *tert*-butyl 3-(1-(1-azabicyclo[1.1.0]butan-3-yl)-1-hydroxyethyl)-1H-indole-1-carboxylate, **197d** (0.25 mmol). The crude reaction mixture was purified by flash column chromatography (98:2 → 80:20 pentane/ethyl acetate) to give **241d** (96 mg, 94% yield) as a white solid.

R_F 0.10 (90:10 pentane/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 2981, 2871, 1697, 1452, 1372, 1245, 1227, 1147; **HRMS** (ESI): Calcd. for $C_{20}H_{21}F_3N_2O_4Na^+$ ([M+Na]$^+$) *m*/*z* 433.1346, found *m*/*z* 433.1360;

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.17 (br. d, $^3J_{HH}$ = 8.3, 1H, C_hH), 7.70 (s, 1H, C_dH), 7.37 (ddd, $^3J_{HH}$ = 8.3, 7.1, $^4J_{HH}$ = 1.3, 1H, C_jH), 7.23 (ddd, $^3J_{HH}$ = 8.0, 7.1, $^4J_{HH}$ = 1.0, 1H, C_iH), 7.15 (dt, $^3J_{HH}$ = 8.0, $^4J_{HH}$ = 1.0, 1H, C_gH), 5.19 (d, $^2J_{HH}$ = 9.2, 1H), 4.67 (d, $^2J_{HH}$ = 10.3, 1H), 4.53 (d, $^2J_{HH}$ = 10.3, 2H), 4.50 (d, $^2J_{HH}$ = 9.2, 1H), 2.08 (s, 3H, C(O)OCH_3), 1.71 (s, 9H, C(CH_3)$_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 203.9 (CH_3C(O)C_b), 156.8 (q, $^2J_{HH}$ = 37.9, CF_3C(O)NR_2), 149.5 (R_2NC(O)OR), 136.2 (C_f), 127.6 (C_e), 125.8 (C_j), 123.8 (C_d), 123.6 (C_i), 119.2 (C_g), 118.0 (C_b), 116.1 (q, $^1J_{HH}$ = 287.7, CF_3), 116.0 (C_h), 85.0 (R_2NC(O)OC(CH_3)$_3$), 58.2 (q, $^3J_{HH}$ = 2.3, C_a), 55.3 (C_a), 48.7 (C_b), 28.4 ((CH_3)$_3$), 24.8 (C(O)OCH_3); **^{19}F NMR** ($CDCl_3$, 377 MHz) δ –72.62.

***tert*-Butyl 3-(3-acetyl-1-((trifluoromethyl)sulfonyl)azetidin-3-yl)-1H-indole-1-carboxylate, 244d**

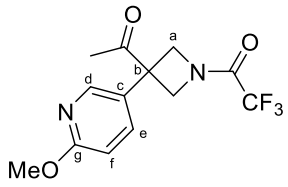


Prepared following general procedure G using the crude *tert*-butyl 3-(1-(1-azabicyclo[1.1.0]butan-3-yl)-1-hydroxyethyl)-1H-indole-1-carboxylate, **197d** (0.25 mmol). The crude reaction mixture was purified by flash column chromatography (DCM) to give **244d** (96 mg, 86% yield) as a white solid.

R_F 0.46 (DCM); **IR** (film) ν_{max}/cm^{-1}: 2981, 2870, 1718, 1453, 1373, 1152; **HRMS** (ESI): Calcd. for $C_{19}H_{21}F_3N_2O_5SNa^+$ ([M+Na]$^+$) *m*/*z* 469.1015, found *m*/*z* 469.1013;

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.17 (br. d, $^3J_{HH}$ = 8.4, 1H, C_hH), 7.69 (s, 1H, C_dH), 7.38 (ddd, $^3J_{HH}$ = 8.4, 7.2, $^4J_{HH}$ = 1.1, 1H, C_jH), 7.23 (ddd, $^3J_{HH}$ = 7.9, 7.2, $^4J_{HH}$ = 1.0, 1H, C_iH), 7.13 (dt, $^3J_{HH}$ = 7.9, $^4J_{HH}$ = 1.1, 1H, C_gH), 4.87 (d, $^2J_{HH}$ = 7.9, 2H, 2 × C_aH), 4.49 (d, $^2J_{HH}$ = 7.9, 2H, 2 × C_aH), 2.08 (s, 3H, C(O)CH_3), 1.72 (s, 9H, C(CH_3)$_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 203.1 (CH_3C(O)C_b), 149.4 (R_2NC(O)C(CH_3)$_3$), 136.0 (C_f), 127.3 (C_e), 125.7 (C_j), 123.6 (C_j), 123.6 (C_i), 119.9 (q, $^1J_{CF}$ = 322.7, CF_3), 119.1 (C_g), 117.4 (C_b), 116.0 (C_h), 85.0 (R_2NC(O)OC(CH_3)$_3$), 58.2 (2 × C_a), 47.6 (C_b), 28.3 ((CH_3)$_3$), 24.6 (C(O)OC(CH_3)$_3$); **^{19}F NMR** ($CDCl_3$, 377 MHz) δ –75.21.

1-(3-Acetyl-3-(6-methoxypyridin-3-yl)azetidin-1-yl)-2,2,2-trifluoroethan-1-one, 241e

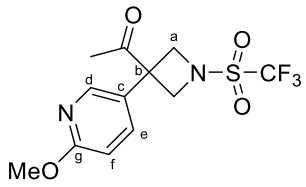


Prepared following general procedure F using the crude 1-(1-azabicyclo[1.1.0]butan-3-yl)-1-(6-methoxypyridin-3-yl)ethan-1-ol, **197e** (0.25 mmol). The crude reaction mixture was purified by flash column chromatography (98:2 → 80:20 pentane/acetone) to give **241e** (53 mg, 70% yield) as a colourless oil.

R_F 0.09 (90:10 pentane/acetone); **IR** (film) ν_{max}/cm^{-1}: 2952, 2925, 1698, 1606, 1497, 1380, 1294, 1257,1206, 1151; **HRMS** (ESI): Calcd. for $C_{13}H_{13}F_3N_2O_3Na^+$ ([M+Na]$^+$) *m*/*z* 325.0770, found *m*/*z* 325.0786;

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.07 (dd, $^4J_{HH}$ = 2.7, $^5J_{HH}$ = 0.8, 1H, C_dH), 7.37 (dd, $^3J_{HH}$ = 8.7, $^4J_{HH}$ = 2.7, 1H, C_eH), 6.80 (dd, $^3J_{HH}$ = 8.7, $^5J_{HH}$ = 0.8, 1H, C_fH), 5.07 (dt, $^2J_{HH}$ = 9.6, $^4J_{HH}$ = 1.3, 1H, C_aH), 4.65 (d, $^2J_{HH}$ = 10.6, 1H, C_aH), 4.52 (dt, $^2J_{HH}$ = 9.9, $^4J_{HH}$ = 1.3, 1H, C_aH), 4.48 (d, $^2J_{HH}$ = 10.6, 1H, C_aH), 3.93 (s, 3H, OCH_3), 2.08 (s, 3H, RC(O)CH_3); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 203.4 (CH_3C(O)C_b), 164.2 (C_g), 156.5 (q, $^2J_{CF}$ = 37.8, R_2NC(O)CF_3), 144.9 (C_d), 136.5 (C_e), 126.1 (C_c), 116.0 (q, $^1J_{CF}$ = 288.1, CF_3), 112.1 (C_f), 58.7 (q, $^1J_{CF}$ = 2.4, C_a), 55.6 (C_a), 53.9 (OCH_3), 52.1 (C_b), 24.6 (RC(O)CH_3); **^{19}F NMR** ($CDCl_3$, 377 MHz) δ –72.68.

1-(3-(6-Methoxypyridin-3-yl)-1-((trifluoromethyl)sulfonyl)azetidin-3-yl)ethan-1-one, 244e



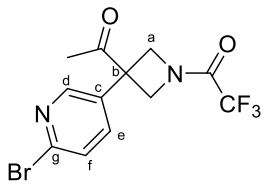
Prepared following general procedure G using the crude 1-(1-azabicyclo[1.1.0]butan-3-yl)-1-(6-methoxypyridin-3-yl)ethan-1-ol, **197e** (0.25 mmol). The crude reaction mixture was purified by flash column chromatography (98:2 → 85:15 pentane/acetone) then

further purified by flash column chromatography (100:0 → 95:5 DCM/ethyl acetate) to give **244e** (57 mg, 67% yield) as a white solid.

R_F 0.46 (95:5 DCM/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 2988, 2852, 1709, 1612, 1497, 1380, 1297, 1227, 1195; **HRMS** (ESI): Calcd. for $C_{12}H_{13}F_3N_2O_4SNa^+$ ([M+Na]$^+$) *m*/*z* 361.0440, found *m*/*z* 361.0458

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.05 (dd, $^4J_{HH}$ = 2.7, $^5J_{HH}$ = 0.8, 1H, C_dH), 7.35 (dd, $^3J_{HH}$ = 8.7, $^4J_{HH}$ = 2.7, 1H, C_eH), 6.81 (dd, $^3J_{HH}$ = 8.7, $^5J_{HH}$ = 0.8, 1H, C_fH), 4.79 (d, $^2J_{HH}$ = 8.1, 2H, 2 × C_aH), 4.46 (d, $^2J_{HH}$ = 8.1, 2H, 2 × C_aH), 3.95 (s, 3H, OCH_3), 2.08 (s, 3H, RC(O)CH_3); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 202.7 (CH_3C(O)C_b), 164.3 (C_g), 144.7 (C_d), 136.3 (C_e), 125.6 (C_c), 119.8 (q, $^1J_{CF}$ = 322.2, CF_3), 112.2 (C_f), 58.6 (2 × C_a), 53.9 (OCH_3), 50.9 (C_b), 24.6 (RC(O)CH_3); **^{19}F NMR** ($CDCl_3$, 377 MHz) δ –75.15.

1-(3-Acetyl-3-(6-bromopyridin-3-yl)azetidin-1-yl)-2,2,2-trifluoroethan-1-one, 241f

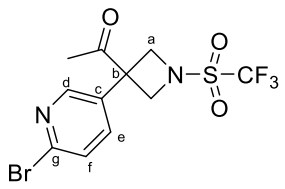


Prepared following general procedure F using the crude 1-(1-azabicyclo[1.1.0]butan-3-yl)-1-(6-bromopyridin-3-yl)ethan-1-ol, **197f** (0.25 mmol). The crude reaction mixture was purified by flash column chromatography (95:5 DCM/ethyl acetate) then further purified by flash column chromatography (95:5 → 80:20 pentane/acetone) to give **241f** (51 mg, 58% yield) as a colourless oil.

R_F 0.25 (80:20 pentane/acetone); **IR** (film) ν_{max}/cm^{-1}: 2956, 1693, 1456, 1366, 1205, 1148; **HRMS** (ESI): Calcd. for $C_{12}H_{10}BrF_3N_2O_2Na^+$ ([M+Na]$^+$) *m*/*z* 372.9770, found *m*/*z* 372.9792.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.30 (dd, $^4J_{HH}$ = 2.8, $^5J_{HH}$ = 0.8, 1H, C_dH), 7.57 (dd, $^3J_{HH}$ = 8.3, $^5J_{HH}$ = 0.8, 1H, C_fH), 7.40 (dd, $^3J_{HH}$ = 8.3, $^4J_{HH}$ = 2.7, 1H, C_eH), 5.10 (dt, $^2J_{HH}$ = 9.9, $^4J_{HH}$ = 1.0, 1H, C_aH), 4.69 (dd, $^2J_{HH}$ = 10.6, $^4J_{HH}$ =1.0, 1H, C_aH), 4.56 (d, $^2J_{HH}$ = 9.9, 1H, C_aH), 4.50 (d, $^2J_{HH}$ = 10.6, 1H, C_aH), 2.11 (s, 3H, CH_3); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 202.2 (CH_3C(O)C_b), 156.4 (q, $^2J_{CF}$ = 38.0, R_2NC(O)CF_3), 148.1 (C_d), 142.6 (C_c), 136.5 (C_e), 132.9 (C_g), 128.9 (C_f), 115.9 (q, $^1J_{CF}$ = 288.1, CF_3), 58.6 (q, $^1J_{CF}$ = 2.7, C_a), 55.5 (C_a), 52.3 (C_b), 24.9 (CH_3); **^{19}F NMR** ($CDCl_3$, 377 MHz) δ –72.53.

1-(3-(6-Bromopyridin-3-yl)-1-((trifluoromethyl)sulfonyl)azetidin-3-yl)ethan-1-one, 244f

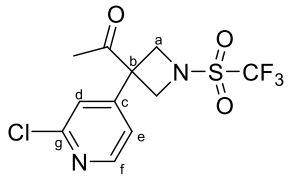


Prepared following general procedure G using the crude 1-(1-azabicyclo[1.1.0]butan-3-yl)-1-(6-bromopyridin-3-yl)ethan-1-ol, **197f** (0.25 mmol). The crude reaction mixture was purified by flash column chromatography (98:2 → 85:15 pentane/acetone) then further purified by flash column chromatography (95:5 DCM/ethyl acetate) to give **244f** (52 mg, 54% yield) as a white solid.

R$_F$ 0.39 (95:5 DCM/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 2981, 2872, 1715, 1580, 1557, 1459, 1379, 1230, 1196; **HRMS** (ESI): Calcd. for $C_{11}H_{10}BrF_3N_2O_3SNa^+$ ([M+Na]$^+$) *m*/*z* 408.9440, found *m*/*z* 408.9452.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.28 (d, $^4J_{HH}$ = 2.7, 1H, C_dH), 7.59 (dd, $^3J_{HH}$ = 8.4, $^5J_{HH}$ = 0.8, 1H, C_fH), 7.37 (dd, $^3J_{HH}$ = 8.4, $^4J_{HH}$ = 2.7, 1H, C_eH), 4.82 (d, $^2J_{HH}$ = 8.3, 2H, 2 × C_aH), 4.49 (d, $^2J_{HH}$ = 8.2, 2H, 2 × C_aH), 2.12 (s, 3H, CH_3); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 201.6 (CH_3C(O)C_b), 147.9 (C_d), 142.8 (C_c), 136.3 (C_e), 132.5 (C_g), 129.1 (C_f), 119.7 (q, $^1J_{CF}$ = 322.0, CF_3), 58.5 (2 × C_a), 51.2 (C_b), 24.9 (CH_3); **^{19}F NMR** ($CDCl_3$, 377 MHz) δ –75.23.

1-(3-(2-Chloropyridin-4-yl)-1-((trifluoromethyl)sulfonyl)azetidin-3-yl)ethan-1-one, 244g

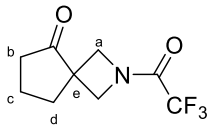


Prepared following general procedure G using the crude 1-(1-azabicyclo[1.1.0]butan-3-yl)-1-(2-chloropyridin-4-yl)ethan-1-ol, **197g** (0.25 mmol). The crude reaction mixture was purified by flash column chromatography (95:5 → 75:25 pentane/acetone) to give **244g** (20 mg, 23% yield) as a white solid.

R$_F$ 0.38 (80:20 pentane/acetone); **IR** (film) ν_{max}/cm^{-1}: 2967, 2944, 1720, 1591, 1543, 1466, 1380, 1225, 1194; **HRMS** (ESI): Calcd. for $C_{11}H_{10}F_3ClN_2O_3SNa^+$ ([M+Na]$^+$) *m*/*z* 343.0126, found *m*/*z* 343.0120;

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.49 (dd, $^3J_{HH}$ = 5.2, $^5J_{HH}$ = 0.7, 1H, C_fH), 7.19 (dd, $^4J_{HH}$ = 1.7, $^5J_{HH}$ = 0.7, 1H, C_dH), 7.06 (dd, $^3J_{HH}$ = 5.2, $^4J_{HH}$ = 1.7, 1H), 4.79 (d, $^2J_{HH}$ = 8.30, 2H, 2 × C_aH), 4.47 (d, $^2J_{HH}$ = 8.30, 2H, 2 × C_aH), 2.12 (s, 3H, CH_3); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 200.7 (CH_3C(O)C_b), 153.3 (C_g), 151.1 (C_f), 149.1 (C_c), 121.8 (C_d), 119.7 (q, $^1J_{CF}$ = 322.2, CF_3), 119.7 (C_g), 58.1 (2 × C_a), 52.5 (C_b), 24.9 (CH_3); **^{19}F NMR** ($CDCl_3$, 377 MHz) δ –75.28.

2-(2,2,2-Trifluoroacetyl)-2-azaspiro[3.4]octan-5-one, 241h

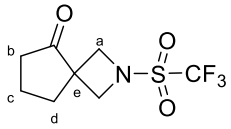


Prepared following general procedure F using the crude 1-(1-azabicyclo[1.1.0]butan-3-yl)cyclobutan-1-ol, **197h** (0.25 mmol). The crude reaction mixture was purified by flash column chromatography (95:5 → 30:70 pentane/ethyl acetate) to give **241h** (30 mg, 54% yield) as a colourless oil.

R_F 0.18 (70:30 petroleum ether/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 2978, 2872, 1741, 1694, 1464, 1253, 1199, 1143; **HRMS** (ESI): Calcd. for $C_9H_{11}F_3NO_2^+$ ($[M+H]^+$) *m*/*z* 222.0736, found *m*/*z* 222.0731;

^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.47 (d, $^2J_{HH}$ = 9.3, 1H, C_aH), 4.18 (d, $^2J_{HH}$ = 10.2, 1H, C_aH), 4.14 (d, $^2J_{HH}$ = 9.3, 1H, C_aH), 3.89 (d, $^2J_{HH}$ = 10.2, 1H, C_aH), 2.36 – 2.18 (m, 4H, C_bH_2, C_dH_2), 1.96 – 1.88 (m, 2H, C_cH_2); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 216.7 ($C_bC(O)C_e$), 156.4 (q, $^2J_{CF}$ = 37.9, $CF_2C(O)NR_2$), 116.1 (q, $^1J_{CF}$ = 289.0, CF_3), 59.0 (q, $^4J_{CF}$ = 2.2, C_a), 56.7 (C_a), 45.6 (C_e), 36.9 (C_b), 34.9 (C_d), 19.3 (C_c); **^{19}F NMR** ($CDCl_3$, 377 MHz) δ –72.56.

2-((Trifluoromethyl)sulfonyl)-2-azaspiro[3.4]octan-5-one, 244h

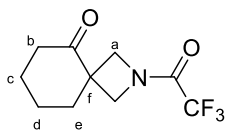


Prepared following general procedure G using the crude 1-(1-azabicyclo[1.1.0]butan-3-yl)cyclobutan-1-ol, **197h** (0.25 mmol). The crude reaction mixture was purified by flash column chromatography (95:5 → 50:50 pentane/ethyl acetate) to give **244h** (56 mg, 87% yield) as a white solid.

R_F 0.20 (70:30 petroleum ether/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 2978, 2873, 1734, 1380, 1218, 1193, 1155, 1178, 1088; **HRMS** (ESI): Calcd. for $C_8H_{10}F_3NO_3SNa^+$ ($[M+Na]^+$) *m*/*z* 280.0226, found *m*/*z* 280.0216;

^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.30 (d, $^2J_{HH}$ = 7.5, 2H, 2 × C_aH), 3.95 (d, $^2J_{HH}$ = 7.5, 2H, 2 × C_aH), 2.29 (t, $^3J_{HH}$ = 7.8, 2H, C_bH_2), 2.27 (t, $^3J_{HH}$ = 6.8, 2H, C_dH_2), 1.91 (m, 2H, C_cH_2); **^{13}C NMR** ($CDCl_3$, 126 MHz) δ 215.7 ($C_bC(O)C_e$), 120.0 (q, $^1J_{CF}$ = 325.4, CF_3), 59.5 (2 × C_a), 44.5 (C_e), 36.8 (C_b), 34.8 (C_d), 19.2 (C_c).; **^{19}F NMR** ($CDCl_3$, 377 MHz) δ –74.98.

2-(2,2,2-Trifluoroacetyl)-2-azaspiro[3.5]nonan-5-one, 241i

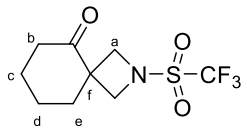


Prepared following general procedure F using the crude 1-(1-azabicyclo[1.1.0]butan-3-yl)cyclopentan-1-ol, **197i** (0.25 mmol). The crude reaction mixture was purified by flash column chromatography (95:5 → 75:25 pentane/ethyl acetate) to give **241i** (26 mg, 44% yield) as a colourless oil.

R_F 0.14 (80:20 petroleum ether/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: redo, 2944, 2863, 1695, 1465, 1448, 1250, 1200, 1145; **HRMS** (ESI): Calcd. for $C_{10}H_{13}F_3NO_2^+$ ($[M+H]^+$) *m*/*z* 236.0893, found *m*/*z* 236.0891;

^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.72 (d, $^2J_{HH}$ = 9.5, 1H, C_aH), 4.30 (d, $^2J_{HH}$ = 10.4, 1H, C_aH), 3.97 (d, $^2J_{HH}$ = 9.5, 1H, C_aH), 3.85 (d, $^2J_{HH}$ = 10.4, 1H, C_aH), 2.39 (t, J = 6.6, 2H, C_bH_2), 2.22 – 2.10 (m, 1H, C_eH), 2.04 (ddd, $^2J_{HH}$ = 13.4, $^3J_{HH}$ = 8.2, 4.6, 1H, C_eH), 1.98 – 1.89 (m, 1H, C_cH), 1.89 – 1.71 (m, 3H, C_cH, C_dH_2); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 207.6 (C_bC(O)C_f), 156.8 (q, $^2J_{CF}$ = 37.5, CF_3C(O)NR_2), 116.1 (q, $^1J_{CF}$ = 288.1, CF_3), 57.5 (q, $^4J_{CF}$ = 2.3, C_a), 55.6 (C_a), 47.0 (C_f), 38.7 (C_b), 37.4 (C_e), 26.7 (C_c), 21.9 (C_d); **^{19}F NMR** ($CDCl_3$, 377 MHz) δ –72.68.

2-((Trifluoromethyl)sulfonyl)-2-azaspiro[3.5]nonan-5-one, 244i

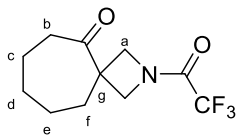


Prepared following general procedure G using the crude 1-(1-azabicyclo[1.1.0]butan-3-yl)cyclopentan-1-ol, **197i** (0.25 mmol). The crude reaction mixture was purified by flash column chromatography (98:2 → 80:20 pentane/ethyl acetate) to give **244i** (39 mg, 58% yield) as a white solid.

R_F 0.24 (80:20 petroleum ether/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 2924, 2861, 1714, 1384, 1187, 1220; **HRMS** (ESI): Calcd. for $C_9H_{12}F_3NO_3SNa^+$ ($[M+Na]^+$) *m*/*z* 294.0382, found *m*/*z* 294.0390;

^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.48 (d, $^2J_{HH}$ = 7.6, 2H, 2 × C_aH), 3.87 (d, $^2J_{HH}$ = 7.8, 2H, 2 × C_aH), 2.39 (t, $^3J_{HH}$ = 6.8, 2H, C_bH_2), 2.15 – 2.08 (m, 2H, C_eH_2), 1.87 (qd, $^3J_{HH}$ = 6.8, 3.1, 2H, C_cH_2), 1.79 – 1.65 (m, 2H, C_dH_2); **^{13}C NMR** ($CDCl_3$, 126 MHz) δ 206.9 (C_bC(O)C_f), 120.1 (q, $^1J_{CF}$ = 322.7, CF_3), 58.2 (2 × C_a), 46.0 (C_f), 38.9 (C_b), 37.3 (C_e), 26.8 (C_c), 22.0 (C_d); **^{19}F NMR** ($CDCl_3$, 377 MHz) δ –74.85.

2-(2,2,2-Trifluoroacetyl)-2-azaspiro[3.6]decan-5-one, 241j

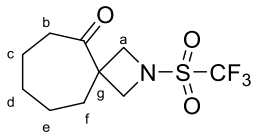


Prepared following general procedure F using the crude 1-(1-azabicyclo[1.1.0]butan-3-yl)cyclohexan-1-ol, **197j** (0.25 mmol). The crude reaction mixture was purified by flash column chromatography (95:5 → 60:40 pentane/ethyl acetate) to give **244j** (17 mg, 27% yield) as a colourless oil.

R_F 0.16 (80:20 petroleum ether/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 2933, 2869, 1698, 1463, 1255, 1202, 1144; **HRMS** (ESI): Calcd. for $C_{11}H_{15}F_3NO_2^+$ ($[M+Na]^+$) *m*/*z* 250.1049, found *m*/*z* 250.1059;

^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.64 (dt, $^2J_{HH}$ = 9.3, $^4J_{HH}$ = 1.3, 1H, C_aH), 4.27 (d, $^2J_{HH}$ = 10.3, 1H, C_aH), 4.02 (dt, $^2J_{HH}$ = 9.3, $^4J_{HH}$ = 1.3, 1H, C_aH), 3.87 (d, $^2J_{HH}$ = 10.3, 1H, C_aH), 2.70 – 2.51 (m, 2H, C_bH_2), 2.15 – 1.99 (m, 2H, C_fH_2), 1.74 – 1.54 (m, 6H, C_cH_2, C_dH_2, C_eH_2); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 211.6 ($C_bC(O)C_g$), 156.7 (q, $^2J_{CF}$ = 37.2, $CF_3C(O)NR_2$), 116.2 (q, $^1J_{CF}$ = 287.4, CF_3), 59.8 (q, $^4J_{CF}$ = 2.2, C_a), 56.6 (C_a), 49.0 (C_g), 41.8 (C_b), 35.6 (C_f), 29.2 (C_c), 25.5 (C_e), 24.5 (C_d); **^{19}F NMR** ($CDCl_3$, 377 MHz) δ –72.53.

2-((Trifluoromethyl)sulfonyl)-2-azaspiro[3.6]decan-5-one, 244j

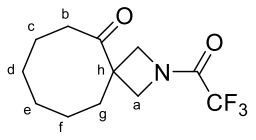


Prepared following general procedure G using the crude 1-(1-azabicyclo[1.1.0]butan-3-yl)cyclohexan-1-ol, **197j** (0.25 mmol). The crude reaction mixture was purified by flash column chromatography (95:5 → 60:40 pentane/ethyl acetate) to give **244j** (35 mg, 50% yield) as a white solid.

R_F 0.31 (80:20 petroleum ether/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 2932, 2860, 1701, 1453, 1385, 1208; **HRMS** (ESI): Calcd. for $C_{10}H_{15}F_3NO_3S^+$ ($[M+H]^+$) *m*/*z* 286.0719, found *m*/*z* 286.0720;

^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.43 (d, $^2J_{HH}$ = 7.7, 2H, 2 × C_aH), 3.89 (d, $^2J_{HH}$ = 7.7, 2H, 2 × C_aH), 2.60 (m, 2H, C_bH_2), 2.09 (m, 2H, C_fH_2), 1.66 – 1.58 (m, 6H, C_cH_2, C_dH_2, C_eH_2); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 210.84 ($C_bC(O)C_g$), 120.05 (q, $^1J_{CF}$ = 322.3, CF_3), 59.69 (2 × C_a), 47.97 (C_g), 41.69 (C_b), 35.27 (C_f), 29.04 (C_c), 25.42 (C_e), 24.43 (C_d); **^{19}F NMR** ($CDCl_3$, 377 MHz) δ -74.87.

2-(2,2,2-Trifluoroacetyl)-2-azaspiro[3.7]undecan-5-one, 241k



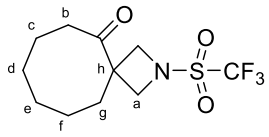
Prepared following general procedure F using the crude 1-(1-azabicyclo[1.1.0]butan-3-yl)cycloheptan-1-ol, **197k** (0.25 mmol). The crude reaction mixture was purified by flash column chromatography (95:5 → 70:30 pentane/ethyl acetate) to give **241k** (27 mg, 41% yield) as a white solid.

R_F 0.20 (80:20 petroleum ether/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 2930, 2860, 1696, 1467, 1253, 1201, 1147; **HRMS** (ESI): Calcd. for $C_{12}H_{16}F_3NO_2Na^+$ ($[M+Na]^+$) *m*/*z* 286.1025, found *m*/*z* 286.1029;

^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.64 (d, $^2J_{HH}$ = 9.4, 1H, C_aH), 4.24 (d, $^2J_{HH}$ = 10.4, 1H, C_aH), 4.04 (d, $^2J_{HH}$ = 9.4, 1H, C_aH), 3.85 (d, $^2J_{HH}$ = 10.4, 1H, C_aH), 2.54 (ddd, $^2J_{HH}$ = 12.4, $^3J_{HH}$ = 8.9, 4.4, 1H, C_bH), 2.45 (ddd, $^2J_{HH}$ = 12.4, $^3J_{HH}$ = 7.9, 4.4, 1H, C_bH), 2.33 (dt, $^2J_{HH}$ = 14.7, $^3J_{HH}$ = 6.1, 1H, C_gH), 2.23 (dt, $^2J_{HH}$ = 14.7, $^3J_{HH}$ = 5.6, 1H, C_gH), 1.86 – 1.77 (m, 2H, C_cH_2),

1.59 – 1.48 (m, 4H, C_fH_2, C_dH_2), 1.44 – 1.35 (m, 1H, C_eH), 1.26 – 1.15 (m, 1H C_eH); **^{13}C NMR** ($CDCl_3$, 126 MHz) δ 213.4 ($C_bC(O)C_h$), 156.8 (q, $^2J_{CF}$ = 37.5, $CF_3C(O)NR_2$), 116.1 (q, $^1J_{CF}$ = 288.1, CF_3), 57.4 (q, $^4J_{CF}$ = 2.3, C_a), 55.3 (C_a), 49.7 (C_h), 38.0 (C_b), 34.5 (C_g), 27.8 (C_c), 25.8 (C_d), 24.3 (C_e), 23.2 (C_f); **^{19}F NMR** ($CDCl_3$, 377 MHz) δ –72.63.

2-((Trifluoromethyl)sulfonyl)-2-azaspiro[3.7]undecan-5-one, 244k

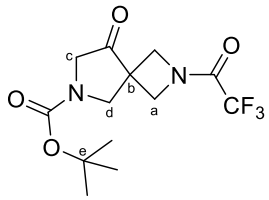


Prepared following general procedure G using the crude 1-(1-azabicyclo[1.1.0]butan-3-yl)cycloheptan-1-ol, **197k** (0.25 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 → 90:10 pentane/acetone) to give **244k** (54 mg, 71% yield) as a white solid.

R_F 0.35 (80:20 petroleum ether/acetone); **IR** (film) ν_{max}/cm^{-1}: 2948, 2864, 1698, 1381, 1224, 1194; **HRMS** (ESI): Calcd. for $C_{11}H_{16}F_3NO_3SNa^+$ ([M+Na]$^+$) *m*/*z* 3220695, found *m*/*z* 322.0714;

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.41 (dd, $^2J_{HH}$ = 7.9, $^4J_{HH}$ = 1.0, 2H, 2 × C_aH), 3.90 (dd, $^2J_{HH}$ = 7.8, $^4J_{HH}$ = 1.0, 2H, 2 × C_aH), 2.48 (m, 2H, C_bH_2), 2.29 (m, 2H, C_gH_2), 1.80 (m, 2H, C_cH_2), 1.55 (m, 4H, C_fH_2, C_dH_2), 1.29 (m, 2H, C_eH_2); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 212.7 ($C_bC(O)C_h$), 120.0 (q, $^1J_{CF}$ = 322.7, CF_3), 58.0 (C_a), 47.6 (C_h), 38.1 (C_b), 34.5 (C_g), 27.5 (C_c), 25.9 (C_d), 24.3 (C_e), 22.9 (C_f); **^{19}F NMR** ($CDCl_3$, 377 MHz) δ –74.92.

***tert*-Butyl 8-oxo-2-(2,2,2-trifluoroacetyl)-2,6-diazaspiro[3.4]octane-6-carboxylate, 241l**



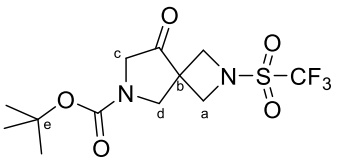
Prepared following general procedure F using the crude *tert*-butyl 3-(1-azabicyclo[1.1.0]butan-3-yl)-3-hydroxyazetidine-1-carboxylate, **197l** (0.25 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 → 85:15 DCM/ethyl acetate) to give **241l** (38 mg, 48% yield) as a white solid.

R_F 0.23 (90:10 DCM/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 2972, 1764, 1589, 1458, 1402, 1262, 1201, 1147; **HRMS** (APCI): Calcd. for $C_{13}H_{17}N_2O_4F_3Na^+$ ([M+H]$^+$) *m*/*z* 345.1033, found *m*/*z* 345.1042.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.56 (d, $^2J_{HH}$ = 9.5, 1H, C_aH), 4.30 (d, $^2J_{HH}$ = 10.4, 2H, 2 × C_aH), 4.05 (d, $^2J_{HH}$ = 10.8, 1H, C_aH), 4.01 – 3.97 (m, C_dH_2), 3.90 (d, $^2J_{HH}$ = 20.2, C_cH), 3.85 (d, $^2J_{HH}$ = 20.2, C_cH), 1.47 (s, 9H, 3 × CH_3); **^{13}C NMR** ($CDCl_3$, 126 MHz) δ 209.1 (br., $C_cC(O)C_b$), 156.3 (q, $^1J_{CF}$ = 37.8, $R_2NC(O)R$), 115.9 (q, $^1J_{CF}$ = 288.5, CF_3), 81.4 (C_e), 58.6 (q, $^1J_{CF}$ = 2.5,

C$_a$), 56.2 (*C*$_a$), 52.9 (br., *C*$_c$), 52.1 (br., *C*$_d$), 45.0 (br., *C*$_b$), 28.4 (C(*C*H$_3$)$_3$); **^{19}F NMR** (CDCl$_3$, 377 MHz) δ –72.70.

***tert*-Butyl 8-oxo-2-((trifluoromethyl)sulfonyl)-2,6-diazaspiro[3.4]octane-6-carboxylate, 244l**

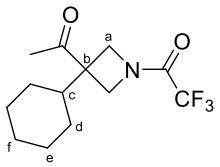


Prepared following general procedure G using the crude *tert*-butyl 3-(1-azabicyclo[1.1.0]butan-3-yl)-3-hydroxyazetidine-1-carboxylate, **197l** (0.25 mmol). The crude reaction mixture was purified by flash column chromatography (98:2 → 85:15 pentane/acetone) and then further purified by flash column chromatography (100:0 → 90:10 DCM/ethyl acetate) to give **244l** (56 mg, 63% yield) as a white solid.

R$_F$ 0.50 (90:10 DCM/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 2974, 1766, 1696, 1682, 1415, 1384, 1194; **HRMS** (ESI): Calcd. for $C_{12}H_{17}F_3N_2O_5SNa^+$ ([M+Na]$^+$) *m*/*z* 381.0702, found *m*/*z* 381.0709.

^{1}H NMR (CDCl$_3$, 400 MHz) δ 4.39 (d, $^2J_{HH}$ = 8.0, 2H, 2 × C$_a$*H*), 4.10 (d, $^2J_{HH}$ = 8.0, 2H, 2 × C$_a$*H*), 3.99 (s, 2H, C$_c$*H*$_2$), 3.86 (s, 2H, C$_d$*H*$_2$), 1.47 (s, 9H, 3 × C*H*$_3$); **^{13}C NMR** (CDCl$_3$, 101 MHz) δ 208.3 (br., C$_c$*C*(O)C$_b$), 154.0 (R$_2$N*C*(O)R) , 119.8 (q, $^1J_{CF}$ = 322.2, *C*F$_3$), 81.5 (*C*$_e$), 58.8 (2 × *C*$_a$), 53.0 (br., *C*$_c$), 52.0 (br., *C*$_d$), 43.9 (br., *C*$_b$), 28.4 (C(*C*H$_3$)$_3$); **^{19}F NMR** (CDCl$_3$, 377 MHz) δ –75.07.

1-(3-Acetyl-3-cyclohexylazetidin-1-yl)-2,2,2-trifluoroethan-1-one, 241m



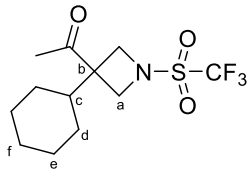
Prepared following general procedure F using the crude 1-(1-azabicyclo[1.1.0]butan-3-yl)-1-cyclohexylethan-1-ol, **197m** (0.25 mmol) with the following alteration: the reaction was stirred for 15 minutes at –78 °C then 30 minutes at 0 °C. The crude reaction mixture was purified by flash column chromatography (100:0 → 80:20 pentane/acetone) to give **241m** (18 mg, 26% yield) as a colourless oil.

R$_F$ 0.13 (90:10 pentane/acetone); **IR** (film) ν_{max}/cm^{-1}: 2929, 2856, 1697, 1469, 1359, 1248, 1202, 1149; **HRMS** (ESI): Calcd. for $C_{13}H_{18}NO_2F_3Na^+$ ([M+Na]$^+$) *m*/*z* 300.1182, found *m*/*z* 300.1194;

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.46 (d, $^2J_{HH}$ = 9.8, 1H, C$_a$*H*), 4.14 (d, $^2J_{HH}$ = 9.9, 1.2, 1H, C$_a$*H*), 4.11 (d, $^2J_{HH}$ = 11.5, 1H, C$_a$*H*), 4.00 (d, $^2J_{HH}$ = 10.9, 1H, C$_a$*H*), 2.10 (s, 3H, C*H*$_3$),

1.84 – 1.70 (m, 3H, C_cH, 2 × C_eH), 1.72 – 1.61 (m, 2H, C_fH, C_dH), 1.55 (m, 1H, C_dH), 1.28 – 1.04 (m, 3H, 2 × C_eH, C_fH), 0.94 (app. dqd, $^2J_{HH}$ = 20.9, $^3J_{HH}$ = 12.6, 3.5, 2H, 2 × C_dH); **^{13}C NMR** ($CDCl_3$, 126 MHz) δ 207.1 ($CH_3C(O)C_b$), 156.5 (q, $^2J_{CF}$ = 37.8, $CF_3C(O)NR_2$), 116.1 (q, $^1J_{CF}$ = 288.5, CF_3), 54.6 (q, $^4J_{CF}$ = 2.5, C_a), 52.3 (C_a), 41.4 (C_c), 27.4 (C_d), 27.1 (C_d), 26.3 (C_e), 26.2 (C_e), 26.0 (C_f), 25.8 (CH_3).

1-(3-Cyclohexyl-1-((trifluoromethyl)sulfonyl)azetidin-3-yl)ethan-1-one, 244m

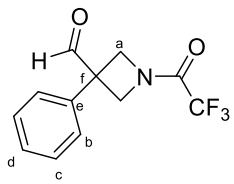


Prepared following general procedure G using the crude 1-(1-azabicyclo[1.1.0]butan-3-yl)-1-cyclohexylethan-1-ol, **197m** (0.25 mmol) with the following alteration: the reaction was stirred for 15 minutes at –78 °C then 30 minutes at 0 °C. The crude reaction mixture was purified by flash column chromatography (100:0 → 98:2 DCM/ethyl acetate) to give **244m** (76 mg, 97% yield) as a white solid.

R_F 0.72 (98:2 DCM/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 2933. 2857, 1702, 1379, 1209, 1197, 1177; **HRMS** (ESI): Calcd. for $C_{12}H_{18}F_3NO_3SNa^+$ ($[M+Na]^+$) *m*/*z* 336.0852, found *m*/*z* 336.0867;

^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.31 (d, $^2J_{HH}$ = 8.3, 2H, 2 × C_aH), 4.08 (d, $^2J_{HH}$ = 8.3, 2H, 2 × C_aH), 2.15 (s, 3H, CH_3), 1.91 – 1.77 (m, 3H, C_cH, 2 × C_eH), 1.77 – 1.63 (m, 3H, C_fH, 2 × C_dH), 1.27 (app. qt, $^2J_{HH}$ = 12.5, $^3J_{HH}$ = 12.5, 3.2, 2H, 2 × C_eH), 1.16 (app. tt, $^3J_{HH}$ = 12.9, 3.1, 1H, C_fH), 1.02 (app. qd, $^2J_{HH}$ = 12.5, $^3J_{HH}$ = 12.5, 3.4, 2H, 2 × C_dH); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 206.43 ($CH_3C(O)C_b$), 119.90 (q, $^1J_{CF}$ = 322.3, CF_3), 55.12 (2 × C_a), 52.77 (C_b), 41.28 (C_c), 27.18 (2 × C_d), 26.23 (2 × C_e), 25.97 (C_f), 25.71 (CH_3); **^{19}F NMR** ($CDCl_3$, 377 MHz) δ –75.47.

3-Phenyl-1-(2,2,2-trifluoroacetyl)azetidine-3-carbaldehyde, 241n

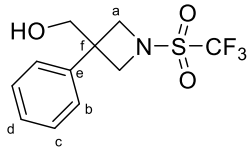


Prepared following general procedure F using the crude (1-azabicyclo[1.1.0]butan-3-yl)(phenyl)methanol, **197n** (0.25 mmol). The crude reaction mixture was purified by flash column chromatography with florisil (30 – 60 mesh) as the stationary phase (95:5 → 70:30 pentane/ethyl acetate) to give **241n** (33 mg, 51% yield) as a colourless oil.

R_F 0.33 (70:30 pentane/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 2969, 2922, 1736, 1365, 1228, 1216, 1206; **HRMS** (APCI): Calcd. for $C_{12}H_{10}F_3NO_2^+$ ($[M+H]^+$) *m*/*z* 258.0736, found *m*/*z* 258.0729;

^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.61 (s, 1H, RC(O)*H*), 7.52 – 7.44 (m, 2H, 2 × C_c*H*), 7.44 – 7.37 (m, 1H, C_d*H*), 7.20 – 7.14 (m, 2H, 2 × C_b*H*), 5.04 (dt, $^{2}J_{HH}$ = 9.5, $^{4}J_{HH}$ = 1.2, 1H, C_a*H*), 4.69 (dd, $^{2}J_{HH}$ = 10.5, $^{4}J_{HH}$ = 1.2, 1H, C_a*H*), 4.62 (d, $^{2}J_{HH}$ = 9.5, 1H, C_a*H*), 4.45 (d, $^{2}J_{HH}$ = 10.5, 1H, C_a*H*); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 194.8 (H*C*(O)C_f), 156.5 (q, $^{2}J_{CF}$ = 37.9, CF_3*C*(O)NR_2), 135.2 (*C_e*), 129.8 (2 × *C_c*), 128.9 (*C_d*), 126.5 (2 × *C_b*), 116.0 (q, $^{1}J_{CF}$ = 288.1, *C*F_3), 56.9 (q, $^{3}J_{CF}$ = 2.5, *C_a*), 54.4 (C_a), 52.7 (*C_f*); **^{19}F NMR** ($CDCl_3$, 377 MHz) δ –72.64.

(3-Phenyl-1-((trifluoromethyl)sulfonyl)azetidin-3-yl)methanol, 244n

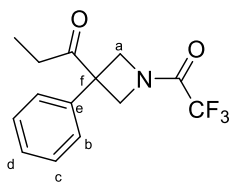


Prepared following general procedure G using the crude (1-azabicyclo[1.1.0]butan-3-yl)(phenyl)methanol, **197n** (0.25 mmol). Due to instability of the aldehyde on silica, the crude reaction mixture was oxidised prior to purification. The crude mixture was dissolved in anhydrous methanol (2.5 mL) under an inert atmosphere and cooled to 0 °C before the addition of sodium borohydride (19 mg, 0.5 mmol, 2.0 equiv). The reaction was stirred for 1 hour at 0 °C and a further 45 minutes at room temperature before the addition of water (10 mL) and ethyl acetate (10 mL). The phases were separated, and the aqueous phase was extracted with diethyl ether (3 × 10 mL) and the combined organic phases were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography (95:5 → 60:40 pentane/ethyl acetate) to give **244n** (62 mg, 82% yield) as a colourless oil.

R_F 0.35 (70:30 pentane/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 3391, 2969, 2871, 1382, 1219, 1193; **HRMS** (ESI): Calcd. for $C_{11}H_{12}F_3NO_3SNa^+$ ([M+Na]$^+$) *m*/*z* 318.0382, found *m*/*z* 318.0395;

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42 (ddd, $^{3}J_{HH}$ = 7.8, 6.3, $^{4}J_{HH}$ = 1.4, 2H, 2 × C_c*H*), 7.37 – 7.31 (m, 1H, C_d*H*), 7.13 – 7.08 (m, 2H, 2 × C_b*H*), 4.47 (d, $^{2}J_{HH}$ = 8.1, 2H, 2 × C_a*H*), 4.42 (d, $^{2}J_{HH}$ = 7.7, 2H, 2 × C_a*H*), 3.87 (s, 2H, RC*H_2*OH), 1.82 (br. s, 1H, O*H*); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 140.7 (*C_e*), 129.8 (2 × *C_c*), 127.9 (*C_d*), 126.0 (2 × *C_b*), 120.0 (q, $^{1}J_{CF}$ = 322.4, *C*F_3) 68.8 (R*C*H_2OH), 59.4 (2 × *C_a*), 43.6 (*C_f*); **^{19}F NMR** ($CDCl_3$, 377 MHz) δ –75.26.

1-(3-Phenyl-1-(2,2,2-trifluoroacetyl)azetidin-3-yl)propan-1-one, 241o



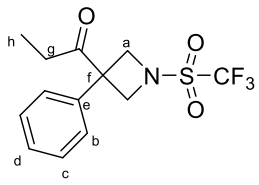
Prepared following general procedure F using the crude 1-(1-azabicyclo[1.1.0]butan-3-yl)-1-phenylpropan-1-ol, **197o** (0.25 mmol). The crude reaction mixture was purified by flash column chromatography

(95:5 → 80:20 pentane/ethyl acetate) to give **241o** (63 mg, 88% yield) as a colourless oil.

R_F 0.12 (90:10 pentane/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 2981, 2870, 1697, 1467, 1203, 1145; **HRMS** (ESI): Calcd. for $C_{14}H_{14}F_3NO_2Na^+$ ([M+Na]$^+$) *m*/*z* 308.0869, found *m*/*z* 308.0870;

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.45 – 7.39 (m, 2H, 2 × C_cH), 7.38 – 7.32 (m, 1H, C_dH), 7.22 – 7.17 (m, 2H, 2 × C_bH), 5.11 (d, $^2J_{HH}$ = 9.5, 1H, C_aH), 4.65 (d, $^2J_{HH}$ = 10.6, 1H, C_aH), 4.58 (d, $^2J_{HH}$ = 9.6, 1H, C_aH), 4.54 (d, $^2J_{HH}$ = 10.6, 1H, C_aH), 2.44 – 2.20 (m, 2H, CH_2CH_3), 0.96 (t, $^3J_{HH}$ = 7.2, 3H, CH_3); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 206.9 (Et*C*(O)C_f), 156.4 (q, $^2J_{CF}$ = 37.8, CF_3C(O)NR_2), 138.1 (C_e), 129.5 (2 × C_c), 128.4 (C_d), 126.2 (2 × C_b), 116.0 (q, $^1J_{CF}$ = 288.4, CF_3), 59.0 (q, $^4J_{CF}$ = 2.6, C_a), 55.8 (C_a), 53.8 (C_f), 30.3 (CH_3), 8.10 (CH_2CH_3); **^{19}F NMR** ($CDCl_3$, 377 MHz) δ –72.56.

1-(3-Phenyl-1-((trifluoromethyl)sulfonyl)azetidin-3-yl)propan-1-one, 244o

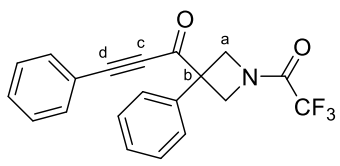


Prepared following general procedure G using the crude 1-(1-azabicyclo[1.1.0]butan-3-yl)-1-phenylpropan-1-ol, **197o** (0.25 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 → 85:15 pentane/ethyl acetate) to give **244o** (50 mg, 62% yield) as a colourless oil.

R_F 0.28 (90:10 pentane/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 2981, 2870, 1716, 1387, 1192, 1225, 1142; **HRMS** (ESI): Calcd. for $C_{13}H_{14}F_3NO_3SNa^+$ ([M+Na]$^+$) *m*/*z* 344.0539, found *m*/*z* 344.0537;

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.48 – 7.41 (m, 2H, 2 × C_cH), 7.40 – 7.34 (m, 1H, C_dH), 7.20 – 7.14 (m, 2H, 2 × C_bH), 4.81 (d, $^2J_{HH}$ = 8.0, 2H, 2 × C_aH), 4.53 (d, $^2J_{HH}$ = 8.0, 2H, 2 × C_aH), 2.32 (q, $^3J_{HH}$ = 7.3, 2H, CH_2CH_3), 0.98 (t, *J* = 7.2, 3H, CH_3); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 206.3 (Et*C*(O)C_f), 137.7 (C_e), 129.7 (2 × C_c), 128.6 (C_d), 126.0 (2 × C_b), 119.9 (q, $^1J_{CF}$ = 322.4, CF_3), 59.0 (C_a), 52.8 (C_f), 30.4 (CH_2CH_3), 8.2 (CH_3); **^{19}F NMR** ($CDCl_3$, 377 MHz) δ –75.14.

3-Phenyl-1-(3-phenyl-1-(2,2,2-trifluoroacetyl)azetidin-3-yl)prop-2-yn-1-one, 241p

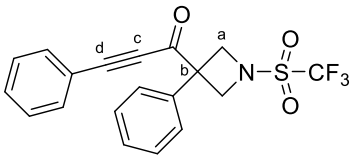


Prepared following general procedure F using the crude 1-(1-azabicyclo[1.1.0]butan-3-yl)-1,3-diphenylprop-2-yn-1-ol, **197p** (0.25 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 → 80:20 pentane/ethyl acetate) to give **241p** (81 mg, 91% yield) as a yellow solid.

R_F 0.55 (80:20 pentane/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 3062, 2955, 2884, 2194, 1698, 1668, 1466, 1264, 1244; **HRMS** (ESI): Calcd. for $C_{20}H_{15}F_3NO_2^+$ ([M+H]$^+$) *m*/*z* 380.0869, found *m*/*z* 380.0878;

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.51 – 7.43 (m, 5H, ArC*H*), 7.42 – 7.36 (m, 3H, ArC*H*), 7.33 – 7.29 (m, 2H, ArC*H*), 5.21 (dt, $^2J_{HH}$ = 9.7, $^4J_{HH}$ = 1.3, 1H, C$_a$*H*), 4.92 (dd, $^2J_{HH}$ = 10.7, $^4J_{HH}$ = 1.1, 1H, C$_a$*H*), 4.75 (dq, $^2J_{HH}$ = 9.8, $^4J_{HH}$ = 1.0, 1H, C$_a$*H*), 4.61 (d, $^2J_{HH}$ = 10.7, 1H, C$_a$*H*); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 184.0 (C$_c$*C*(O)C$_b$), 156.5 (q, $^2J_{CF}$ = 37.8, CF_3*C*(O)NR_2), 137.2 (Ar*C*), 133.4 (Ar*C*H), 131.7 (Ar*C*H), 129.5 (Ar*C*H), 129.0 (Ar*C*H), 128.8 (Ar*C*H), 127.0 (Ar*C*H), 119.2 (Ar*C*), 116.2 (q, $^1J_{CF}$ = 288.0, *C*F_3), 97.3 (*C$_d$*), 84.9 (*C$_c$*), 59.2 (q, $^1J_{CF}$ = 2.0, *C$_a$*), 56.6 (*C$_a$*), 54.8 (*C$_b$*); **^{19}F NMR** ($CDCl_3$, 377 MHz) δ –72.59.

3-Phenyl-1-(3-phenyl-1-((trifluoromethyl)sulfonyl)azetidin-3-yl)prop-2-yn-1-one, 244p

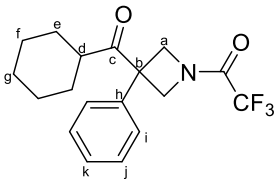


Prepared following general procedure G using the crude 1-(1-azabicyclo[1.1.0]butan-3-yl)-1,3-diphenylprop-2-yn-1-ol, **197p** (0.25 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 → 80:20 pentane/ethyl acetate) to give **244p** (88 mg, 89% yield) as a yellow solid.

R_F 0.40 (90:10 pentane/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 2965, 2870, 2199, 1668, 1383, 1229, 1198; **HRMS** (ESI): Calcd. for $C_{19}H_{14}F_3NO_3SNa^+$ ([M+Na]$^+$) *m*/*z* 416.0539, found *m*/*z* 416.0527;

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.52 – 7.43 (m, 5H, ArC*H*)), 7.43 – 7.35 (m, 3H, ArC*H*)), 7.31 – 7.25 (m, 2H, ArC*H*)), 4.98 (d, $^2J_{HH}$ = 8.1, 2H, 2 × C$_a$*H*), 4.65 (d, $^2J_{HH}$ = 8.1, 2H, 2 × C$_a$*H*); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 183.2 (C$_c$*C*(O)C$_b$), 136.6 (Ar*C*), 133.3 (Ar*C*H), 131.7 (Ar*C*H), 129.5 (Ar*C*H), 128.9 (Ar*C*H), 128.9 (Ar*C*H), 126.7 (Ar*C*H), 119.9 (q, $^1J_{CF}$ = 322.2, *C*F_3), 119.1 (Ar*C*), 97.3 (*C$_d$*), 84.7 (*C$_c$*), 59.3 (2 × *C$_a$*), 53.6 (*C$_b$*); **^{19}F NMR** ($CDCl_3$, 377 MHz) δ –75.29.

1-(3-(Cyclohexanecarbonyl)-3-phenylazetidin-1-yl)-2,2,2-trifluoroethan-1-one, 241q

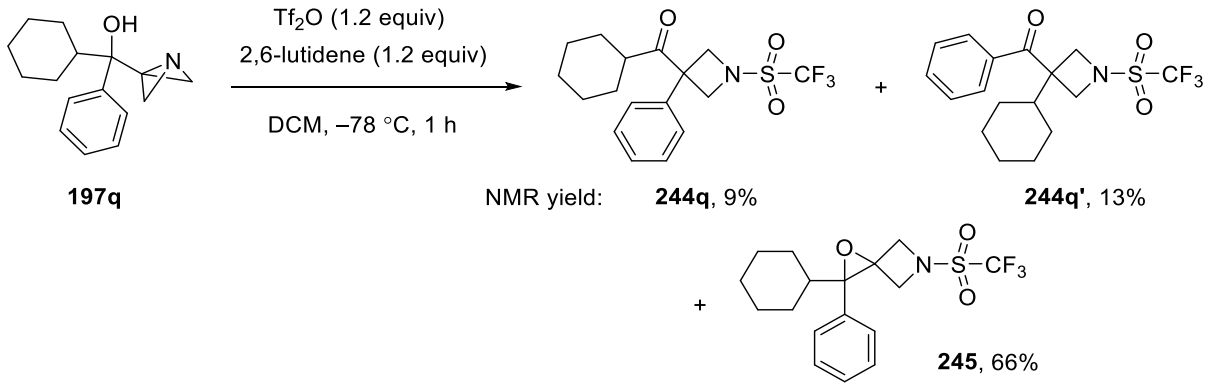


Prepared following general procedure F using the crude (1-azabicyclo[1.1.0]butan-3-yl)(cyclohexyl)(phenyl)methanol, **197q** (0.25 mmol). The crude reaction mixture was purified by flash column chromatography (98:2 → 80:20 DCM/ethyl acetate) to give **241q** (22 mg, 26% yield) as a colourless oil.

R$_F$ 0.42 (90:10 DCM/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 2933, 2858, 1698, 1467, 1449, 1238, 1203, 1146; **HRMS** (ESI): Calcd. for $C_{18}H_{20}F_3NO_2Na^+$ ([M+Na]$^+$) *m*/*z* 362.1338, found *m*/*z* 362.1349;

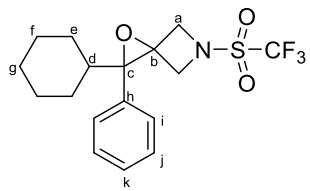
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.47 – 7.39 (m, 2H, 2 × C_jH), 7.39 – 7.33 (m, 1H, C_kH), 7.24 – 7.19 (m, 2H, C_iH), 5.13 (dt, $^2J_{HH}$ = 9.5, $^4J_{HH}$ = 1.3, 1H, C_aH), 4.66 (d, $^2J_{HH}$ = 10.7, 1H, C_aH), 4.55 (dt, $^2J_{HH}$ = 9.4, $^4J_{HH}$ = 1.2, 2H, C_aH), 2.46 (tt, $^3J_{HH}$ = 10.1, $^3J_{HH}$ = 3.3, 1H, C_dH), 1.73 – 1.63 (m, 2H, 2 × C_fH), 1.63 – 1.52 (m, 2H, 2 × C_fH), 1.39 (m, 2H, 2 × C_eH), 1.30 – 1.20 (m, 1H, C_eH), 1.09 (m, 3H, C_eH, C_gH_2); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 209.0 (C_c), 156.5 (d, $^2J_{CF}$ = 37.6, $R_2NC(O)CF_3$), 137.4 (C_h), 129.5 (2 × C_i), 128.5 (C_k), 126.4 (2 × C_j), 116.1 (d, $^1J_{CF}$ = 288.1, CF_3), 58.8 (C_a), 55.3 (C_a), 54.2 (C_b), 46.7 (C_d), 30.3 (C_e), 30.2 (C_e), 25.5 (2 × C_f, C_g); **^{19}F NMR** ($CDCl_3$, 377 MHz) δ –72.52.

Semipinacol rearrangement of 197q with Tf$_2$O



Following general procedure G using the crude (1-azabicyclo[1.1.0]butan-3-yl)(cyclohexyl)(phenyl)methanol, **197q** (0.25 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 → 90:10 DCM/ethyl acetate), mixed fractions were further purified by flash column chromatography (99:1 → 60:40 pentane/DCM).

2-Cyclohexyl-2-phenyl-5-((trifluoromethyl)sulfonyl)-1-oxa-5-azaspiro[2.3]hexane, 245

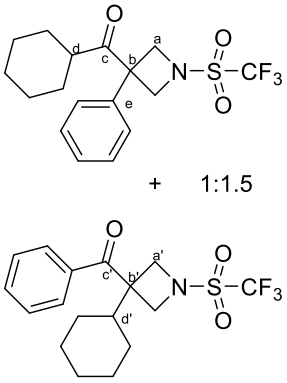


Mixed fractions were discarded and **245** was isolated as a white solid (30 mg, 32% yield).

R$_F$ 0.51 (50:50 pentane/DCM); **IR** (film) ν_{max}/cm^{-1}: 2930, 2855, 1446, 1377, 1226, 1195; **HRMS** (ESI): Calcd. for $C_{17}H_{20}F_3NO_3SNa^+$ ([M+Na]$^+$) *m*/*z* 398.1021, found *m*/*z* 398.1023;

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39 – 7.29 (m, 3H, C_iH, C_kH), 7.27 – 7.21 (m, 2H, C_jH), 4.66 (d, $^{2}J_{HH}$ = 10.0, 1H, C_aH), 4.56 (d, $^{2}J_{HH}$ = 10.0, 1H, C_aH), 4.14 (d, $^{2}J_{HH}$ = 10.2, 1H, C_aH), 4.08 (d, $^{2}J_{HH}$ = 10.2, 1H, C_aH), 1.91 – 1.67 (m, 4H, 2 × C_eH, C_fH, C_gH), 1.67 – 1.53 (m, 1H, C_gH), 1.33 – 1.10 (m, 4H, C_eH, 2 × C_fH, C_dH), 1.00 – 1.69 (m, C_eH, C_fH); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 134.4 (C_h), 128.4 (C_k), 128.3 (2 × C_i), 127.5 (2 × C_j), 120.0 (d, $^{1}J_{HH}$ = 322.6), 69.7 (C_c), 63.5 (C_b), 59.6 (C_a), 59.3 (C_a), 43.6 (C_d), 29.4 (C_e), 27.8 (C_e), 26.2 (C_f), 25.9 (C_f), 25.7 (C_g); **^{19}F NMR** ($CDCl_3$, 377 MHz) δ –74.82.

Cyclohexyl(3-phenyl-1-((trifluoromethyl)sulfonyl)azetidin-3-yl)methanone, 244q and (3-cyclohexyl-1-((trifluoromethyl)sulfonyl)azetidin-3-yl)(phenyl)methanone, 244q'

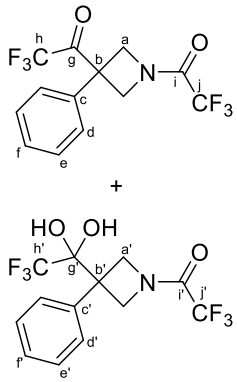


Compounds **244q** and **244q'** were isolated as a mixture in a 1:1.5 ratio (22 mg, 23% yield).

R_F 0.33 and 0.29 (95:5 DCM/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 2932, 2855, 1710, 1678, 1448, 1385, 1223, 1192; **HRMS** (ESI): Calcd. for $C_{17}H_{20}F_3NO_3SNa^+$ ($[M+Na]^+$) *m*/*z* 398.1021, found *m*/*z* 398.1008;

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.73 – 7.67 (m, ArC*H*), 7.64 – 7.58 (m, ArC*H*), 7.53 – 7.46 (m, ArC*H*), 7.46 – 7.40 (m, ArC*H*), 7.40 – 7.34 (m, ArC*H*), 7.20 – 7.13 (m, ArC*H*), 4.83 (d, $^{2}J_{HH}$ = 8.0, 2H, 2 × C_aH), 4.62 (d, $^{2}J_{HH}$ = 8.2, 2H, 2 × $C_{a'}H$), 4.52 (d, $^{2}J_{HH}$ = 8.0, 2H, 2 × C_aH), 4.35 (d, $^{2}J_{HH}$ = 8.3, 2H, 2 × $C_{a'}H$), 2.44 (tt, $^{3}J_{HH}$ = 11.4, 3.6, 1H, C_dH), 2.15 – 2.02 (m, 1H, $C_{d'}H$), 1.92 – 1.53 (m, $C_{alkyl}H$), 1.41 – 0.98 (m, $C_{alkyl}H$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 208.3 (C_c), 198.7 ($C_{c'}$), 136.9 (C_e), 134.0 (Ar*C*), 132.8 (Ar*C*), 129.6 (Ar*C*), 129.2 (Ar*C*), 129.1 (Ar*C*), 128.6 (Ar*C*), 126.1 (Ar*C*), 119.9 (q, $^{1}J_{CF}$ = 322.6, *C*F_3), 119.8 (q, $^{1}J_{CF}$ = 321.9, *C*F_3), 58.6 (2 × C_a), 55.7 (2 × $C_{a'}$), 53.2 (C_b), 51.5 ($C_{b'}$), 46.7 (C_d), 41.7 ($C_{d'}$), 30.3 (C_{alkyl}), 26.9 (C_{alkyl}), 26.1 (C_{alkyl}), 25.9 (C_{alkyl}), 25.5 (C_{alkyl}), 25.4 (C_{alkyl}); **^{19}F NMR** ($CDCl_3$, 377 MHz) δ –75.01, –75.61.

1,1'-(3-Phenylazetidine-1,3-diyl)bis(2,2,2-trifluoroethan-1-one), 241r

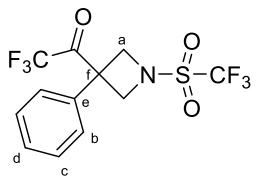


Prepared following general procedure F using the purified 1-(1-azabicyclo[1.1.0]butan-3-yl)-2,2,2-trifluoro-1-phenylethan-1-ol, **197r** (0.25 mmol) with the following alteration: the reaction was stirred for 15 minutes at –78 °C then 30 minutes at 0 °C. The crude reaction mixture was purified by flash column chromatography (95:5 → 60:40 pentane/ethyl acetate) to give **241r** (20 mg, 25% yield) as a white solid. In solution it exists as a mixture of the ketone and the hydrate.

R_F 0.24 (70:30 pentane/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 3380, 2963, 1754, 1697, 1458, 1260, 1204, 1151; **HRMS** (APCI): Calcd. for $C_{13}H_9F_6NO_2^+$ ([M+H]$^+$) *m*/*z* 326.0610, found *m*/*z* 326.0600; Calcd. for $C_{13}H_{11}F_6NO_3^+$ (hydrate [M+H]$^+$) *m*/*z* 344.0716, found *m*/*z* 344.0701;

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.52 – 7.37 (m, 3H, 2 × C_dH, C_fH), 7.31 – 7.26 (m, 2H, 2 × C_eH), 5.18 (d, $^2J_{HH}$ = 10.1, 1H, C_aH), 5.08 (d, $^2J_{HH}$ = 9.9, 1H, $C_{a'}H$), 4.84 (d, $^2J_{HH}$ = 11.2, 1H, C_aH), 4.78 (d, $^2J_{HH}$ = 10.1, 1H, C_aH), 4.70 (d, $^2J_{HH}$ = 9.9, 1H, $C_{a'}H$), 4.67 (d, $^2J_{HH}$ = 11.2, 1H, C_aH), 4.41 (d, $^2J_{HH}$ = 10.7, 1H, C_aH), 4.08 (s, 2H, 2 × O*H*); **^{13}C NMR** (CD_2Cl_2, 126 MHz) δ 188.5 (q, $^2J_{CF}$ = 33.7, C_g), 156.5 (q, $^2J_{CF}$ = 37.9, C_i), 156.1 (q, $^2J_{CF}$ = 36.8, $C_{i'}$), 138.4 ($C_{c'}$), 133.9 (C_c), 130.1 (2 × C_d), 129.8 (C_f), 128.9 (2 × $C_{e'}$), 128.6 (2 × $C_{d'}$), 128.4 (C_f), 127.1 (2 × C_e), 125.8 (q, $^1J_{CF}$ = 268.9, $C_{h'}$), 116.6 (q, $^1J_{CF}$ = 287.7, $C_{j'}$), 116.3 (q, $^1J_{CF}$ = 290.0, C_h), 116.1 (q, $^1J_{CF}$ = 293.7, C_j), 95.4 (q, $^2J_{CF}$ = 30.5, $C_{g'}$), 59.7 ($C_{a'}$), 58.9 (C_a), 57.0 ($C_{a'}$), 55.5 (C_a), 51.6 (C_b), 48.1 ($C_{b'}$).

2,2,2-Trifluoro-1-(3-phenyl-1-((trifluoromethyl)sulfonyl)azetidin-3-yl)ethan-1-one, 244r

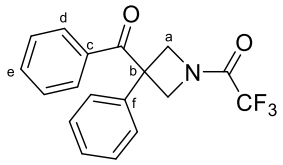


Prepared following general procedure G using the purified 1-(1-azabicyclo[1.1.0]butan-3-yl)-2,2,2-trifluoro-1-phenylethan-1-ol, **197r** (0.25 mmol) with the following alteration: the reaction was stirred for 15 minutes at –78 °C then 30 minutes at 0 °C. The crude reaction mixture was purified by flash column chromatography (100:0 → 70:30 pentane/acetone) to give **244r** (65 mg, 72% yield) as a white solid. In solution it exists as a mixture of the ketone and the hydrate.

R_F 0.22 (80:20 pentane/acetone); **IR** (film) ν_{max}/cm^{-1}: 2982, 1750, 1382, 1229, 1190, 1160; **HRMS** (APCI): Calcd. for $C_{12}H_9F_6NO_3S^+$ ([M+H]$^+$) *m*/*z* 362.0280, found *m*/*z* 362.0273;

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.53 – 7.41 (m, 3H, 2 × C_cH, C_dH), 7.25 – 7.19 (m, 2H, C_bH), 4.91 (d, $^{2}J_{HH}$ = 8.7, 2H, 2 × C_aH), 4.66 (d, $^{2}J_{HH}$ = 8.7, 1H, 2 × C_aH); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 187.8 (q, $^{2}J_{HH}$ = 34.2, $CF_3C(O)C_f$), 133.3 (C_e), 130.1 (2 × C_c), 129.8 (C_d), 126.6 (2 × C_b), 119.9 (d, $^{1}J_{CF}$ = 321.8, RSO_2CF_3), 115.8 (d, $^{1}J_{CF}$ = 293.6, $RC(O)CF_3$), 58.4 (d, $^{3}J_{CF}$ = 1.7, C_a), 50.4 (C_f); **^{19}F NMR** ($CDCl_3$, 377 MHz) δ –71.33, –75.43.

1-(3-benzoyl-3-phenylazetidin-1-yl)-2,2,2-trifluoroethan-1-one, 241s

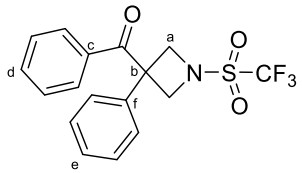


Prepared following general procedure F using the crude (1-azabicyclo[1.1.0]butan-3-yl)diphenylmethanol, **197s** (0.25 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 → 90:10 toluene/acetone) to give **241s** (35 mg, 42% yield) as a colourless oil.

R_F 0.53 (90:10 toluene/acetone); **IR** (film) ν_{max}/cm^{-1}: 2969, 2870, 1696, 1681, 1448, 1469, 1255, 1229, 1204, 1145; **HRMS** (ESI): Calcd. for $C_{18}H_{15}F_3NO_2^+$ ($[M+H]^+$) *m*/*z* 334.1049, found *m*/*z* 334.1050;

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.67 (dd, $^{3}J_{HH}$ = 8.5, $^{4}J_{HH}$ =1.3, 2H, C_dH), 7.51 (tt, $^{3}J_{HH}$ = 7.4, $^{4}J_{HH}$ =1.3, 1H, C_eH), 7.44 – 7.30 (m, 7H, ArCH), 5.22 (d, $^{2}J_{HH}$ = 9.9, 1H, C_aH), 4.81 (d, $^{2}J_{HH}$ = 11.1, 1H, C_aH), 4.70 (d, $^{2}J_{HH}$ = 11.1, 1H, C_aH), 4.64 (dt, $^{2}J_{HH}$ = 9.9, 1.2, 1H, C_aH); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 197.0 (ArC(O)C_b), 156.6 (q, $^{2}J_{CF}$ = 37.8, $CF_3C(O)NR_2$), 139.2 (C_c), 133.9 (ArCH), 132.7 (C_f), 129.8 (ArCH), 129.8 (ArCH), 129.0 (ArCH), 128.4 (ArCH), 125.6 (ArCH), 116.1 (q, $^{1}J_{CF}$ = 288.0, CF_3), 61.0 (C_a), 57.3 (C_a), 52.1 (C_b); **^{19}F NMR** ($CDCl_3$, 377 MHz) δ –72.51.

Phenyl(3-phenyl-1-((trifluoromethyl)sulfonyl)azetidin-3-yl)methanone, 244s

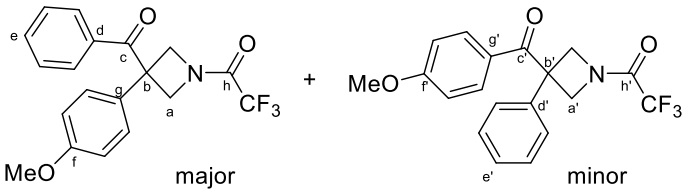


Prepared following general procedure G using the crude (1-azabicyclo[1.1.0]butan-3-yl)diphenylmethanol, **197s** (0.25 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 → 90:10 toluene/acetone) to give **244s** (83 mg, 90% yield) as a white solid.

R_F 0.41 (80:20 petroleum ether/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 2981, 2869, 1673, 1384, 1227, 1197; **HRMS** (ESI): Calcd. for $C_{17}H_{14}F_3NO_3SNa^+$ ($[M+Na]^+$) *m*/*z* 392.0539, found *m*/*z* 392.0544;

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.61 – 7.51 (m, 2H, C_dH), 7.47 – 7.38 (m, 1H, C_dH), 7.37 – 7.23 (m, 7H, Ar*C*H), 4.88 (d, $^{2}J_{HH}$ = 8.2, 2H, 2 × C_aH), 4.49 (d, $^{2}J_{HH}$ = 8.2, 2H, 2 × C_aH); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 196.5 (Ar*C*(O)C_b), 138.8 (C_c), 134.0 (Ar*C*H), 132.6 (C_f), 129.9 (Ar*C*H), 129.7 (Ar*C*H), 129.0 (Ar*C*H), 128.6 (Ar*C*H), 125.5 (Ar*C*H), 119.9 (q, $^{1}J_{CF}$ = 322.6, *C*F_3) 60.6 (2 × C_a), 50.9 (C_b); **^{19}F NMR** ($CDCl_3$, 377 MHz) δ –75.21.

1-(3-Benzoyl-3-(4-methoxyphenyl)azetidin-1-yl)-2,2,2-trifluoroethan-1-one, 241t and 2,2,2-trifluoro-1-(3-(4-methoxybenzoyl)-3-phenylazetidin-1-yl)ethan-1-one, 241t'

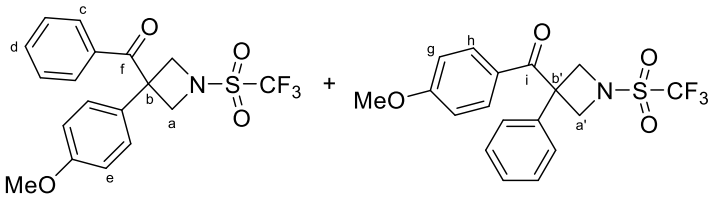


Prepared following general procedure F using the crude (1-azabicyclo[1.1.0]butan-3-yl)(4-methoxyphenyl)(phenyl)methanol, **197t** (0.25 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 → 90:10 pentane/acetone) and further purified by flash column chromatography (90:10 DCM/ethyl actetate) to give a mixture of **241t** and **241t'** in a 1:0.3 ratio respectively (36 mg, 42% yield).

R_F 0.38 (80:20 pentane/acetone); **IR** (film) ν_{max}/cm^{-1}: 2981, 2870, 1698, 1682, 1514, 1467, 1251, 1146; **HRMS** (ESI): Calcd. for $C_{19}H_{17}F_3NO_3^+$ ([M+H]$^+$) *m*/*z* 364.1155, found *m*/*z* 364.1161;

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.67 (dd, $^{3}J_{HH}$ = 8.4, $^{4}J_{HH}$ = 1.2, 2H, 2 × Ar*CH*), 7.64 (d, $^{3}J_{HH}$ = 9.0, 2H, 2 × Ar*CH'*), 7.51 (tt, $^{3}J_{HH}$ = 7.0, $^{4}J_{HH}$ = 1.2, 1H, C_eH), 7.38 (m, 2H, 2 × Ar*CH*), 7.29 (d, $^{3}J_{HH}$ = 8.9, 2H, 2 × Ar*CH*), 6.92 (d, $^{3}J_{HH}$ = 8.9, 2H, 2 × Ar*CH*), 6.84 (d, $^{3}J_{HH}$ = 9.0, 2H, 2 × Ar*CH'*), 5.22 (d, $^{2}J_{HH}$ = 9.8, 1H, $C_{a'}H$), 5.20 (d, *J* = 9.9, 1H, C_aH), 4.80 (d, $^{2}J_{HH}$ = 11.1, 1H, $C_{a'}H$), 4.78 (d, $^{2}J_{HH}$ = 11.0, 1H, C_aH), 4.68 (d, $^{2}J_{HH}$ = 11.1, 1H, $C_{a'}H$), 4.65 (d, $^{2}J_{HH}$ = 10.9, 1H, C_aH), 4.60 (d, $^{2}J_{HH}$ = 9.8, 1H, $C_{a'}H$), 4.59 (d, $^{2}J_{HH}$ = 9.9, 1H, C_aH), 3.82 (OCH_3'), 3.79 (s, 3H, OCH_3); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 197.1 (C_c), 195.5 ($C_{c'}$), 163.9 ($C_{f'}$), 159.5 (C_f), 156.6 (q, $^{2}J_{CF}$ = 37.7, C_h), 156.6 (q, $^{2}J_{CF}$ = 37.8, $C_{h'}$), 139.6 ($C_{g'}$), 133.7 (C_e), 132.7 (C_d), 132.1 (Ar*C*H'), 131.0 (C_g), 129.7 (Ar*C*H), 129.7 (Ar*C*H'), 128.9 (Ar*C*H), 128.2 ($C_{e'}$), 126.8 (Ar*C*H), 125.5 (Ar*C*H'), 115.7 (q, $^{1}J_{CF}$ = 289.0, *C*F_3) 115.1 (Ar*C*H), 114.2 (Ar*C*H'), 61.1 (q, $^{4}J_{CF}$ = 2.2, C_a), 61.1 ($C_{a'}$), 57.4 (C_a), 57.4 ($C_{a'}$), 55.6 (OCH_3'), 55.4 (OCH_3), 51.8 ($C_{b'}$), 51.6 (C_b); **^{19}F NMR** ($CDCl_3$, 377 MHz) δ –72.50.

(3-(4-Methoxyphenyl)-1-((trifluoromethyl)sulfonyl)azetidin-3-yl)(phenyl)methanone, 244t and (4-methoxyphenyl)(3-phenyl-1-((trifluoromethyl)sulfonyl)azetidin-3-yl)methanone 244t'



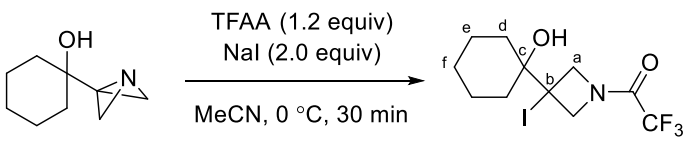
Prepared following general procedure G using the crude (1-azabicyclo[1.1.0]butan-3-yl)(4-methoxyphenyl)(phenyl)methanol, **197t** (0.25 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 → 90:10 pentane/acetone) and further purified by flash column chromatography (90:10 DCM/ethyl actetate) to give a mixture of **244t** and **244t'** in a 1:0.8 ratio respectively (88 mg, 80% yield).

R_F 0.15 (90:10 pentane/acetone); **IR** (film) ν_{max}/cm^{-1}: 2968, 2906, 1676, 1599, 1513, 1386, 1257, 1224, 1203; **HRMS** (ESI): Calcd. for $C_{18}H_{17}F_3NO_4S^+$ ([M+H]$^+$) *m*/*z* 400.0825, found *m*/*z* 400.0840;

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.63 (dd, $^3J_{HH}$ = 8.3, $^4J_{HH}$ = 1.4, 2H, ArC*H*), 7.59 (d, $^3J_{HH}$ = 8.9, 2H, ArC*H*), 7.51 (t, $^3J_{HH}$ = 7.6, 1H, C_eH), 7.43 – 7.24 (m, 9H, ArC*H*), 6.93 (d, $^3J_{HH}$ = 8.9, 2H, ArC*H*), 6.83 (dd, $^3J_{HH}$ = 9.0, $^4J_{HH}$ = 2.4, 2H, ArC*H*), 4.94 (m, 4H, C_aH, C_aH'), 4.53 (m, 4H, C_aH, C_aH'), 3.82 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 196.7 (C_c), 195.1 ($C_{c'}$), 164.0 ($C_{f'}$), 159.6 (C_f), 139.2 ($C_{g'}$), 133.8 (C_e), 132.6 (C_d), 132.1 (Ar*C*H'), 130.6 (C_g), 129.8 (Ar*C*H'), 129.7 (Ar*C*H), 129.0 (Ar*C*H), 128.4 ($C_{e'}$), 126.7 (Ar*C*H), 125.4 (Ar*C*H'), 119.9 (q, $^1J_{CF}$ = 322.4, *C*F_3), 115.2 (Ar*C*H), 114.3 (Ar*C*H'), 60.8 (C_a), 60.7 ($C_{a'}$), 55.6 (O*C*H_3'), 55.4 (O*C*H_3), 50.6 ($C_{b'}$), 50.4 (C_b); **^{19}F NMR** ($CDCl_3$, 377 MHz) δ –75.07.

6.4.8. Attempts to improve the semipinacol rearrangement reaction

2,2,2-Trifluoro-1-(3-(1-hydroxycyclohexyl)-3-iodoazetidin-1-yl)ethan-1-one, 246



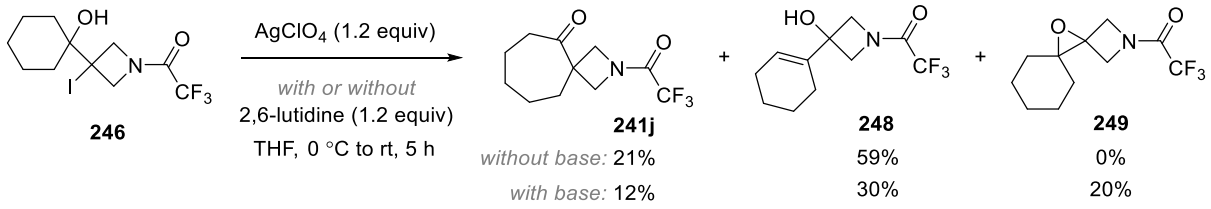
To a round bottom flask containing a mixture of crude **197j** (1.0 mmol, 1.0 equiv) and sodium iodide (300 mg, 2.0 mmol, 2.0 equiv) under an inert atmosphere was added anhydrous acetonitrile (10 mL). The flask was cooled to 0 °C and trifluoroacetic anhydride (0.16 mL, 1.2 mmol, 1.2 equiv) was added and the reaction was stirred for 30 minutes at 0 °C. Saturated

aqueous sodium bicarbonate solution (20 mL) and ethyl acetate (20 mL) were added, and the reaction mixture transferred to a separating funnel. The phases were separated, and the aqueous phase was extracted with ethyl acetate (3 × 20 mL) and the combined organic phases were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography (99:1 → 80:20 pentane/acetone) to give **246** (188 mg, 50% yield) as a colourless oil.

R_F 0.58 (80:20 pentane/acetone); **IR** (film) ν_{max}/cm^{-1}: 3487, 2923, 2860, 1677, 1248, 1201, 1163; **HRMS** (ESI): Calcd. for $C_{11}H_{15}NO_2F_3I^+$ ($[M+H]^+$) *m*/*z* 378.0172, found *m*/*z* 378.0176

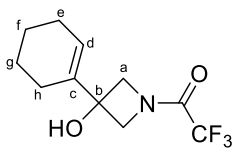
^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.11 (d, $^2J_{HH}$ = 10.9, 1H, C_aH), 4.81 (d, $^2J_{HH}$ = 11.9, 1H, C_aH), 4.69 (dt, $^2J_{HH}$ = 10.8, $^4J_{HH}$ = 1.5, 1H, C_aH), 4.47 (dd, $^2J_{HH}$ = 11.9, $^4J_{HH}$ = 1.8, 1H, C_aH), 2.13 (br. s, 1H, O*H*), 1.83 – 1.44 (m, 9H, 2 × C_eH_2, 2 × C_dH_2, C_fH), 1.14 (dtt, $^2J_{HH}$ = 12.9, $^3J_{HH}$ = 12.9, 3.7, 1H, C_fH); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 156.4 (q, $^2J_{CF}$ = 37.8, $R_2NC(O)CF_3$), 116.0 (d, $^1J_{CF}$ = 288.1, CF_3), 73.8 (C_c), 66.4 (q, $^4J_{CF}$ = 2.3, C_a), 63.7 (C_a), 43.4 (C_b), 32.9 (C_d), 32.4 (C_d), 25.1 (C_f), 21.7 (2 × C_e); **^{19}F NMR** ($CDCl_3$, 377 MHz) δ –72.71.

1-(3-(Cyclohex-1-en-1-yl)-3-hydroxyazetidin-1-yl)-2,2,2-trifluoroethan-1-one and 1-(11-oxa-2-azadispiro[3.0.55.14]undecan-2-yl)-2,2,2-trifluoroethan-1-one



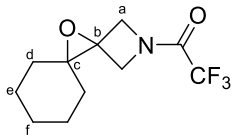
To a round bottom flask containing iodohydrin **246** (0.1 mmol, 1.0 equiv) under an inert atmosphere was added anhydrous THF (1 mL). The flask was cooled to 0 °C before the addition of 2,6-lutidine[A] (14 μL, 0.12 mmol, 1.2 equiv) and silver perchlorate (25 mg, 1.2 mmol, 1.2 equiv). The reaction was warmed to room temperature and stirred overnight. Water (10 mL) and ethyl acetate (10 mL) were added, and the reaction mixture transferred to a separating funnel. The phases were separated, and the aqueous phase was extracted with ethyl acetate (3 × 10 mL) and the combined organic phases were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography (98:2 → 85:15 pentane/acetone) to give three fractions containing: **249**, **241j** and **248**.

Notes: (A) Without the addition of 2,6-lutidine, only **241j** and **248** were isolated.



R_F 0.21 (95:5 pentane/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 3411, 2930, 1685, 1460, 1252, 1204, 1146; **HRMS** (APCI): Calcd. for $C_{11}H_{14}NO_2F_3^+$ ($[M+H]^+$) *m*/*z* 250.1049, found *m*/*z* 250.1049;

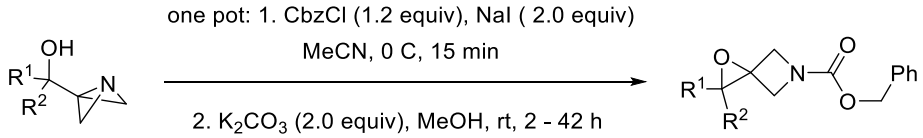
^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.84 (tt, $^3J_{HH}$ = 3.7, $^4J_{HH}$ = 1.6, 1H, C_dH), 4.52 (dt, $^2J_{HH}$ = 10.1, $^4J_{HH}$ = 1.5, 1H, C_aH), 4.38 – 4.24 (m, 2H, 2 × C_aH), 4.05 (dd, $^2J_{HH}$ = 11.0, $^4J_{HH}$ = 1.6, 1H, C_aH), 2.23 (br. s, 1H, O*H*), 2.15 – 2.07 (m, 2H, C_e H_2), 2.06 – 2.02 (m, 2H, C_hH_2), 1.72 – 1.66 (m, 2H, C_gH_2), 1.63 – 1.56 (m, 2H, C_fH_2); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 156.5 (q, $^2J_{CF}$ = 37.4, CF_3C(O)NR_2), 136.7 (C_c), 124.5 (C_d), 116.1 (d, $^1J_{CF}$ = 288.1, CF_3), 73.6 (C_b), 63.0 (q, $^4J_{CF}$ = 1.9, C_a), 60.3 (C_a), 25.0 (C_e), 23.3 (C_h), 22.4 (C_g), 21.9 (C_f); **^{19}F NMR** ($CDCl_3$, 377 MHz) δ –72.53.



R_F 0.67 (80:20 pentane/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 2937, 2862, 1701, 1454, 1259, 1202, 1150; **HRMS** (APCI): Calcd. for $C_{11}H_{14}NO_2F_3^+$ ($[M+H]^+$) *m*/*z* 250.1049, found *m*/*z* 250.1043

^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.57 (dt, $^2J_{HH}$ = 11.0, $^4J_{HH}$ = 1.6, 1H, C_aH), 4.53 (dt, $^2J_{HH}$ = 11.1, 2.0, 1H, C_aH), 4.38 (dd, $^2J_{HH}$ = 12.0, $^4J_{HH}$ = 2.0, 1H, C_aH), 4.31 (d, $^2J_{HH}$ = 12.0, 1H, C_aH), 1.81 – 1.70 (m, 2H, 2 × C_eH), 1.66 – 1.51 (m, 4H, 2 × C_eH, C_fH_2), 1.50 – 1.44 (m, 4H, 2 × C_dH_2); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 156.1 (q, $^2J_{CF}$ = 37.4, CF_3C(O)NR_2), 116.02 (d, $^1J_{CF}$ = 288.1), 64.4 (C_b), 63.7 (C_c), 58.1 (C_a), 55.7 (C_a), 30.9 (C_d), 30.7 (C_d), 25.0 (C_f), 24.5 (C_e), 24.5 (C_e); **^{19}F NMR** ($CDCl_3$, 377 MHz) δ –72.80.

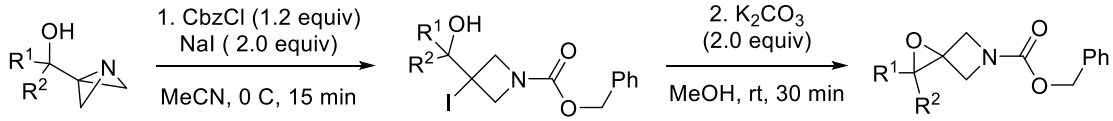
6.4.9. General procedure H for the synthesis of spiro epoxy azetidines



To a round bottom flask containing a mixture of the azabicyclo[1.1.0]butyl carbinol (0.25 mmol, 1.0 equiv) and sodium iodide (75 mg, 0.50 mmol, 2.0 equiv) under an inert atmosphere was added anhydrous acetonitrile (2.5 mL). The flask was cooled to 0 °C and benzyl chloroformate (40 μL, 0.30 mmol, 1.2 equiv) was added with stirring. After 15 minutes at 0 °C, potassium carbonate (69 mg, 0.50 mmol, 2.0 equiv) was added followed by anhydrous methanol (2.5 mL) and the reaction was warmed to room temperature. The progress of the reaction was monitored by TLC and usually found to be complete within 2 hours at room temperature. After the reaction was complete, diethyl ether or ethyl acetate (10 mL) and

saturated aqueous sodium bicarbonate solution (10 mL) were added, and the reaction mixture transferred to a separating funnel. The phases were separated, and the aqueous phase was extracted with diethyl ether or ethyl acetate (3 × 20 mL) and the combined organic phases were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure.

6.4.10. General procedure I for the synthesis of spiro epoxy azetidines

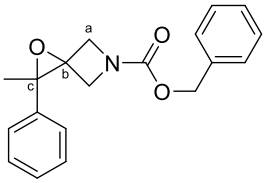


To a round bottom flask containing a mixture of the azabicyclo[1.1.0]butyl carbinol (0.25 mmol, 1.0 equiv) and sodium iodide (75 mg, 0.5 mmol, 2.0 equiv) under an inert atmosphere was added anhydrous acetonitrile (2.5 mL). The flask was cooled to 0 °C and benzyl chloroformate (40 μL, 0.30 mmol, 1.2 equiv) was added with stirring. After 15 minutes at 0 °C, saturated aqueous sodium bicarbonate solution (10 mL) and diethyl ether or ethyl acetate (10 mL) were added, and the reaction mixture transferred to a separating funnel. The phases were separated, and the aqueous phase was extracted with diethyl ether or ethyl acetate (3 × 20 mL) and the combined organic phases were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure.

After isolation and characterisation, the iodohydrin was transferred to a round bottom flask and potassium carbonate (69 mg, 0.50 mmol, 2.0 equiv) was added. Under and inert atmosphere, anhydrous methanol (2.5 mL) was added, and the reaction was stirred at room temperature for 30 minutes. Saturated aqueous sodium bicarbonate solution (10 mL) and diethyl ether or ethyl acetate (10 mL) were added, and the reaction mixture transferred to a separating funnel. The phases were separated, and the aqueous phase was extracted with diethyl ether or ethyl acetate (3 × 20 mL) and the combined organic phases were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure.

6.4.11. Scope of the epoxide formation reaction

Benzyl 2-methyl-2-phenyl-1-oxa-5-azaspiro[2.3]hexane-5-carboxylate, 250a



Prepared following general procedure 3a using the crude 1-(1-azabicyclo[1.1.0]butan-3-yl)-1-phenylethan-1-ol **197a** (0.25 mmol) and CbzCl (40 μL, 1.2 equiv). The crude reaction mixture was purified by

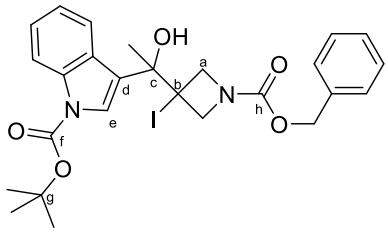
flash column chromatography (98:2 → 85:15 pentane/acetone) to give **250a** (74 mg, 96% yield) as a colourless oil.

R_F 0.5 (80:20 pentane/acetone); **IR** (film) ν_{max}/cm^{-1}: 2959, 2871, 1711, 1445, 1405, 1351; **HRMS** (ESI): Calcd. for $C_{19}H_{19}NO_3Na^+$ ([M+Na]$^+$) *m*/*z* 332.1257, found *m*/*z* 332.1255;

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35 – 7.25 (m, 8H, ArC*H*), 7.25 – 7.17 (m, 2H, ArC*H*), 5.08 (s, 2H, ROCH_2Ph), 4.35 (dd, $^2J_{HH}$ = 10.4, $^4J_{HH}$ = 1.5, 1H, C_aH), 4.26 (ddd, $^2J_{HH}$ = 10.5, $^4J_{HH}$ = 1.6, 0.8, 1H, C_aH), 4.12 (ddd, $^2J_{HH}$ = 10.6, $^4J_{HH}$ = 1.1, 0.8, 1H, C_aH), 3.76 (dd, $^2J_{HH}$ = 10.5, $^4J_{HH}$ = 1.6, 1H, C_aH), 1.63 (s, 3H, CH_3); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 156.3 (R_2NC(O)OR), 138.0 (Ar*C*), 136.5 (Ar*C*), 128.6 (Ar*C*H), 128.6 (Ar*C*H), 128.3 (Ar*C*H), 128.2 (Ar*C*H), 128.0 (Ar*C*H), 125.5 (Ar*C*H), 67.1 (RO*C*H_2Ph), 66.0 (C_b), 62.9 (C_c), 56.2 (br., 2 × C_a), 19.3 (CH_3).

tert-Butyl 3-(1-(1-((benzyloxy)carbonyl)-3-iodoazetidin-3-yl)-1-hydroxyethyl)-1H-indole-1-carboxylate, 8d' and benzyl 2-(1-(_tert_-butoxycarbonyl)-1H-indol-3-yl)-2-methyl-1-oxa-5-azaspiro[2.3]hexane-5-carboxylate, 250d

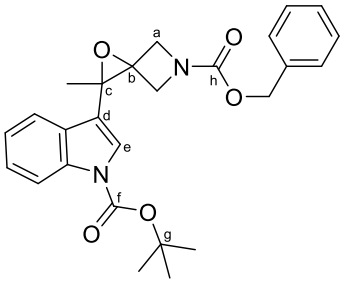
Prepared following general procedure I using the crude *tert*-Butyl 3-(1-(1-azabicyclo[1.1.0]butan-3-yl)-1-hydroxyethyl)-1H-indole-1-carboxylate **197d** (0.25 mmol). The crude reaction mixture was purified by flash column chromatography (98:2 → 85:15 pentane/acetone) and further purified by flash column chromatography (100:0 → 95:5 DCM/methanol) to give **242d** (88 mg, 61% yield) as a colourless oil. After the addition of potassium carbonate and methanol, the crude mixture did not require purification and gave **250d** (69 mg, 62% yield) as a colourless oil.



R_F 0.32 (98:2 pentane/methanol); **IR** (film) ν_{max}/cm^{-1}: 3429, 2977, 1690, 1449, 1368, 1254, 1151; **HRMS** (ESI): Calcd. for $C_{26}H_{29}IN_2O_5Na^+$ ([M+Na]$^+$) *m*/*z* 599.1013, found *m*/*z* 599.0990;

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.06 (d, $^3J_{HH}$ = 8.3, 1H, ArC*H*), 7.85 (d, $^3J_{HH}$ = 7.9, 1H, ArC*H*), 7.59 (s, 1H, C_eH), 7.29 – 7.07 (m, 7H, ArC*H*), 4.93 (s, 2H, ROCH_2Ph), 4.83 (app. d, $^2J_{HH}$ = 10.0, 2H, 2 × C_aH), 4.45 (dd, $^2J_{HH}$ = 10.0, $^4J_{HH}$ = 1.2, 1H, C_aH), 4.33 (dd, $^2J_{HH}$ = 10.3, $^4J_{HH}$ = 1.2, 1H, C_aH), 2.64 (br. s, 1H, O*H*), 1.78 (s, 3H, CH_3), 1.60 (s, 9H, $C_g(CH_3)_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 156.3 (C_h), 149.6 (C_f), 136.3 (Ar*C*), 135.6 (Ar*C*), 128.7 (Ar*C*), 128.6 (Ar*C*), 128.2 (Ar*C*H), 128.0 (Ar*C*H), 124.6 (Ar*C*H), 124.6 (C_e), 122.9 (Ar*C*H), 122.3 (Ar*C*H),

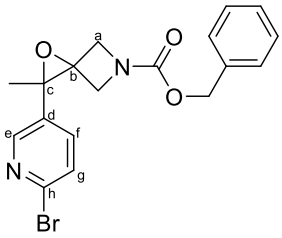
121.5 (*C*$_d$), 115.4 (Ar*C*H), 84.4 (*C*$_g$), 76.2 (*C*$_c$), 67.1 (RO*C*H$_2$Ph), 65.2 (br., 2 × *C*$_a$), 45.3 (*C*$_b$), 28.3 (C$_g$(*C*H$_3$)$_3$), 27.3 (*C*H$_3$).



IR (film) ν_{max}/cm^{-1}: 2978, 1709, 1450, 1372, 1243, 1153; **HRMS** (ESI): Calcd. for $C_{26}H_{28}N_2O_5Na^+$ ([M+Na]$^+$) *m*/*z* 471.1890, found *m*/*z* 471.1907;

^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.16 (d, $^3J_{HH}$ = 8.4, 1H, ArC*H*), 7.65 (dt, $^3J_{HH}$ = 7.9, $^4J_{HH}$ = 1.1, 1H, ArC*H*), 7.53 (s, 1H, C$_e$*H*), 7.33 (m, 6H, ArC*H*), 7.23 (ddd, $^3J_{HH}$ = 8.2, 7.2, $^4J_{HH}$ = 1.1, 1H, ArC*H*), 5.09 (s, 2H, ROC*H*$_2$Ph), 4.42 (dd, $^2J_{HH}$ = 10.4, $^4J_{HH}$ = 1.5, 1H, C$_a$*H*), 4.32 (ddd, $^2J_{HH}$ = 10.4, $^4J_{HH}$ = 1.5, 0.8, 1H, C$_a$*H*), 4.20 (ddd, $^2J_{HH}$ = 10.6, $^4J_{HH}$ = 1.5, 0.8, 1H, C$_a$*H*), 3.88 (dd, $^2J_{HH}$ = 10.6, $^4J_{HH}$ = 1.5, 1H, C$_a$*H*), 1.71 (s, 3H, C*H*$_3$), 1.68 (s, 9H, C$_g$(C*H*$_3$)$_3$); **^{13}C NMR** (CDCl$_3$, 101 MHz) δ 156.3 (*C*$_h$), 149.4 (*C*$_f$), 136.4 (Ar*C*), 135.7 (Ar*C*), 128.6 (Ar*C*H), 128.2 (Ar*C*), 128.2 (Ar*C*H), 128.1 (Ar*C*H), 124.9 (Ar*C*H), 124.0 (*C*$_e$), 123.0 (Ar*C*H), 120.2 (Ar*C*H), 118.5 (*C*$_d$), 115.5 (Ar*C*H), 84.3 (*C*$_g$), 67.1 (RO*C*H$_2$Ph), 65.6 (*C*$_b$), 60.4 (*C*$_c$), 56.3 (br., *C*$_a$), 56.0 (br., *C*$_a$), 28.3 (C$_g$(*C*H$_3$)$_3$), 20.3 (*C*H$_3$).

Benzyl 2-(6-bromopyridin-3-yl)-2-methyl-1-oxa-5-azaspiro[2.3]hexane-5-carboxylate, 250f



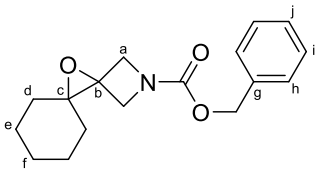
Prepared following general procedure H using the crude 1-(1-azabicyclo[1.1.0]butan-3-yl)-1-(6-bromopyridin-3-yl)ethan-1-ol **197f** (0.25 mmol) and CbzCl (40 μL, 1.2 equiv). The crude reaction mixture was purified by flash column chromatography (95:5 → 80:20 pentane/acetone) to give **250f** (64 mg, 66% yield) as a white solid.

R$_F$ 0.35 (80:20 pentane/acetone); **IR** (film) ν_{max}/cm^{-1}: 2967, 1737, 1715, 1454, 1408, 1353, 1216; **HRMS** (ESI): Calcd. for $C_{18}H_{17}BrN_2O_3Na^+$ ([M+Na]$^+$) *m*/*z* 411.0315, found *m*/*z* 411.0317

^{1}H NMR (CDCl$_3$, 400 MHz) δ 8.30 (dd, $^4J_{HH}$ = 2.5, $^5J_{HH}$ = 0.8, 1H, C$_e$*H*), 7.46 (dd, $^3J_{HH}$ = 8.3, $^5J_{HH}$ = 0.8, 1H, C$_g$*H*), 7.37 (dd, $^3J_{HH}$ = 8.3, $^4J_{HH}$ = 2.5, 1H, C$_f$*H*), 7.35 – 7.28 (m, 5H, ArC*H*), 5.09 (s, 2H, ROC*H*$_2$Ph), 4.36 (dd, $^2J_{HH}$ = 10.5, $^4J_{HH}$ = 1.6, 1H, C$_a$*H*), 4.27 (ddd, $^2J_{HH}$ = 10.5, $^4J_{HH}$ = 0.8, 0.8, 1H, C$_a$*H*), 4.13 (ddd, $^2J_{HH}$ = 10.5, $^4J_{HH}$ = 0.8, 0.8, 1H, C$_a$*H*), 3.77 (dd, $^2J_{HH}$ = 10.5, $^4J_{HH}$ = 1.6, 1H, C$_a$*H*), 1.64 (s, 3H, C*H*$_3$); **^{13}C NMR** (CDCl$_3$, 101 MHz) δ 156.2 (R$_2$N*C*(O)OR), 148.0 (*C*$_e$), 142.0 (*C*$_h$), 136.3 (Ar*C*), 135.8 (*C*$_e$), 133.4 (*C*$_d$), 128.6 (Ar*C*H),

128.3 (Ar*C*H), 128.2 (Ar*C*H), 127.9 (C_g), 67.3 (RO*C*H$_2$Ph), 66.3 (C_c), 60.9 (C_d), 55.9 (br., C_a), 55.8 (br., C_a), 18.9 (*C*H$_3$).

Benzyl 11-oxa-2-azadispiro[3.0.5.1]undecane-2-carboxylate, 250j

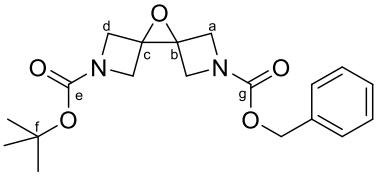


Prepared following general procedure H using the crude 1-(1-azabicyclo[1.1.0]butan-3-yl)cyclohexan-1-ol **197j** (0.25 mmol) and CbzCl (40 μL, 1.2 equiv). The crude reaction mixture was purified by flash column chromatography (95:5 → 80:20 pentane/acetone) to give **250j** (64 mg, 90% yield) as a colourless oil.

R$_F$ 0.35 (80:20 pentane/acetone); **IR** (film) ν_{max}/cm^{-1}: 2933, 2855, 1712, 1448, 1407, 1354, 1216; **HRMS** (ESI): Calcd. for $C_{17}H_{21}NO_3Na^+$ ([M+Na]$^+$) *m*/*z* 310.1414, found *m*/*z* 310.1412;

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42 – 7.28 (m, 2H, ArC*H*), 5.12 (s, 2H, ROC*H*$_2$Ph), 4.22 (d, $^2J_{HH}$ = 11.0, 1H, 2 × C$_a$*H*), 4.17 (d, $^2J_{HH}$ = 11.0, 1H, 2 × C$_a$*H*), 1.79 – 1.67 (m, 2H, 2 × C$_e$*H*), 1.61 – 1.48 (m, 4H, 2 × C$_e$*H*, C$_f$*H*$_2$), 1.46 – 1.40 (m, 4H, 2 × C$_d$*H*$_2$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 156.3 (R$_2$N*C*(O)OR), 136.5 (C_g), 128.5 (Ar*C*H), 128.2 (C_j), 128.1 (Ar*C*H), 67.0 (RO*C*H$_2$Ph), 64.1 (C_b), 64.0 (C_c), 55.9 (br., 2 × C_a), 30.9 (2 × C_d), 25.1 (C_f), 24.6 (2 × C_e).

2-Benzyl 7-(*tert*-butyl) 9-oxa-2,7-diazadispiro[3.0.3^5.1^4]nonane-2,7-dicarboxylate, 250l

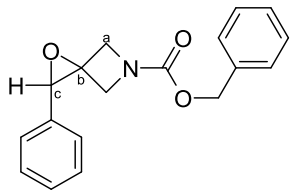


Prepared following general procedure H using the crude *tert*-butyl 3-(1-azabicyclo[1.1.0]butan-3-yl)-3-hydroxyazetidine-1-carboxylate **197l** (0.25 mmol) and CbzCl (40 μL, 1.2 equiv). The crude reaction mixture was purified by flash column chromatography (98:2 → 85:15 pentane/acetone) to give **250l** (82 mg, 91% yield) as a colourless oil.

R$_F$ 0.39 (80:20 pentane/acetone); **IR** (film) ν_{max}/cm^{-1}: 2969. 2942, 1697, 1454, 1390, 1352, 1143; **HRMS** (ESI): Calcd. for $C_{19}H_{24}N_2O_5Na^+$ ([M+Na]$^+$) *m*/*z* 383.1577, found *m*/*z* 383.1583;

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39 – 7.28 (m, 5H, ArC*H*), 5.12 (s, 2H, ROC*H*$_2$Ph), 4.20 (s, 4H, 2 × C$_a$*H*$_2$), 4.11 (s, 2H, 2 × C$_d$*H*$_2$), 1.45 (s, 9H, C$_f$(C*H*$_3$)$_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 156.3 (C_g), 156.0 (C_e), 136.3 (Ar*C*), 128.6 (Ar*C*H), 128.3 (Ar*C*H), 128.2 (Ar*C*H), 80.5 (C_f), 67.3 (RO*C*H$_2$Ph), 61.3 (C_c/C_b), 61.3 (C_c/C_b), 55.7 (br., 2 × C_a), 55.4 (br., 2 × C_a), 28.4 (C$_f$(*C*H$_3$)$_3$).

Benzyl 2-phenyl-1-oxa-5-azaspiro[2.3]hexane-5-carboxylate, 250n



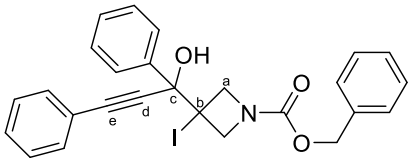
Prepared following general procedure H using the crude (1-Azabicyclo[1.1.0]butan-3-yl)(phenyl)methanol **197n** (0.25 mmol) and CbzCl (40 μL, 1.2 equiv). After the addition of potassium carbonate and methanol, the reaction was stirred for 42 hours at room temperature. The crude reaction mixture was purified by flash column chromatography (95:5 → 80:20 pentane/acetone) to give **250n** (59 mg, 80% yield) as a colourless oil.

R_F 0.46 (80:20 pentane/acetone); **IR** (film) ν_{max}/cm^{-1}: 2945, 1735, 1712, 1446, 1409, 1354, 1217; **HRMS** (ESI): Calcd. for $C_{18}H_{17}NO_3Na^+$ ($[M+H]^+$) *m*/*z* 318.1101, found *m*/*z* 318.1103;

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40 – 7.29 (m, 8H, ArC*H*), 7.17 – 7.10 (m, 2H, ArC*H*), 5.11 (s, 2H, ROCH_2Ph), 4.43 (dd, $^2J_{HH}$ = 10.4, $^4J_{HH}$ = 1.5, 1H, C_aH), 4.36 (d, $^2J_{HH}$ = 10.4, 1H, C_aH), 4.31 (dt, $^2J_{HH}$ = 10.5, $^4J_{HH}$ = 1.0, 1H, C_aH), 4.01 (s, 1H, C_cH), 3.97 (dd, $^2J_{HH}$ = 10.5, $^4J_{HH}$ = 1.6, 1H, C_aH); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 156.2 (R_2NC(O)OR), 136.4 (Ar*C*), 134.5 (Ar*C*), 128.7 (Ar*C*H), 128.7 (Ar*C*H), 128.6 (Ar*C*H), 128.2 (Ar*C*H), 128.2 (Ar*C*H), 125.8 (Ar*C*H), 67.1 (RO*C*H_2Ph), 62.6 (C_b), 60.1 (C_c), 57.2 (br., C_a), 55.9 (br., C_a).

Benzyl 3-(1-hydroxy-1,3-diphenylprop-2-yn-1-yl)-3-iodoazetidine-1-carboxylate, 242p and benzyl 2-phenyl-2-(phenylethynyl)-1-oxa-5-azaspiro[2.3]hexane-5-carboxylate 250p

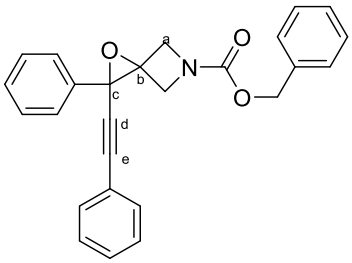
Prepared following general procedure I using the crude 1-(1-azabicyclo[1.1.0]butan-3-yl)-1,3-diphenylprop-2-yn-1-ol **197p** (0.25 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 → 95:5 DCM/ethyl acetate) to give **242p** (121 mg, 98% yield) as a colourless oil. After the addition of potassium carbonate and methanol, the crude mixture did not require purification and gave **250p** (85 mg, 86% yield) as a colourless oil.



R_F 0.46 (95:5 DCM/ethyl acetate); **IR** (film) ν_{max}/cm^{-1}: 3339, 2969, 1737, 1715, 1685, 1420, 1354, 1216; **HRMS** (ESI): Calcd. for $C_{26}H_{22}INO_3Na^+$ ($[M+Na]^+$) *m*/*z* 546.0537, found *m*/*z* 546.0510;

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.70 (dd, $^3J_{HH}$ = 7.4, $^4J_{HH}$ = 2.3, 2H, ArC*H*), 7.51 – 7.41 (m, 2H, ArC*H*), 7.40 – 7.21 (m, 11H, ArC*H*), 5.16 (d, $^2J_{HH}$ = 10.2, 1H, C_aH), 5.09 (d, $^2J_{HH}$ = 10.2, 1H, C_aH), 5.00 (s, 2H, ROCH_2Ph), 4.47 (d, $^2J_{HH}$ = 10.0, 1H, C_aH), 4.45 (d, $^2J_{HH}$ = 10.0, 1H, C_aH), 3.38 (s, 1H, O*H*); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 156.4 (R_2NC(O)OR), 140.5 (Ar*C*), 136.3 (Ar*C*), 132.0 (Ar*C*H), 129.3 (Ar*C*H), 128.9 (Ar*C*H), 128.5 (Ar*C*H), 128.5 (Ar*C*H), 128.2

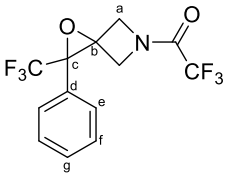
(Ar*C*H), 128.1 (Ar*C*H), 128.0 (Ar*C*H), 127.3 (Ar*C*H), 121.6 (Ar*C*), 88.2 (*C*$_e$), 86.8 (*C*$_d$), 76.7 (*C*$_c$), 67.1 (RO*C*H$_2$Ph), 65.1 (br., 2 × *C*$_a$), 41.4 (*C*$_b$).



IR (film) ν_{max}/cm^{-1}: 2968, 2943, 1712, 1443, 1403, 1352, 1216; **HRMS** (ESI): Calcd. for $C_{26}H_{21}NO_3Na^+$ ([M+Na]$^+$) *m*/*z* 418.1414, found *m*/*z* 418.1428;

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.53 (dd, $^3J_{HH}$ = 7.9, $^4J_{HH}$ = 1.7, 2H, ArC*H*), 7.46 – 7.29 (m, 13H ArC*H*), 5.12 (s, 2H, ROC*H*$_2$Ph), 4.59 (dd, $^2J_{HH}$ = 10.7, $^4J_{HH}$ = 1.6, 1H, C$_a$*H*), 4.43 (ddd, $^2J_{HH}$ = 10.7, $^4J_{HH}$ = 0.7, 1H, C$_a$*H*), 4.29 (ddd, $^2J_{HH}$ = 10.7, $^4J_{HH}$ = 0.7, 1H, C$_a$*H*), 3.91 (dd, $^2J_{HH}$ = 10.7, $^4J_{HH}$ = 1.6 , 1H, C$_a$*H*); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 156.3 (R$_2$N*C*(O)OR), 136.4 (Ar*C*), 134.1 (Ar*C*), 132.3 (Ar*C*H), 129.4 (Ar*C*H), 128.9 (Ar*C*H), 128.7 (Ar*C*H), 128.6 (Ar*C*H), 128.5 (Ar*C*H), 128.3 (Ar*C*H), 128.2 (Ar*C*H), 126.0 (Ar*C*H), 121.5 (Ar*C*), 87.3 (*C*$_e$), 83.8 (*C*$_d$), 68.6 (*C*$_c$), 67.3 (RO*C*H$_2$Ph), 58.3 (*C*$_b$), 56.8 (*C*$_a$), 55.6 (*C*$_a$).

2,2,2-Trifluoro-1-(2-phenyl-2-(trifluoromethyl)-1-oxa-5-azaspiro[2.3]hexan-5-yl)ethan-1-one, 252



Prepared following general procedure H using 1-(1-azabicyclo[1.1.0]butan-3-yl)-2,2,2-trifluoro-1-phenylethan-1-ol **197r** (0.25 mmol) and TFAA (40 μL, 1.2 equiv) in place of CbzCl. The crude reaction mixture was purified by flash column chromatography (99:1 → 85:15 pentane/acetone) to give **252** (40 mg, 49% yield) as a colourless oil.

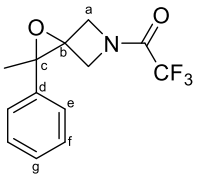
R$_F$ 0.34 (90:10 pentane/methanol); **IR** (film) ν_{max}/cm^{-1}: 2950, 1704, 1514, 1494, 1451, 1333, 1291, 1251, 1141; **HRMS** (APCI): Calcd. for $C_{13}H_9NO_2F_6^+$ ([M+H]$^+$) *m*/*z* 326.0610, found *m*/*z* 326.0619;

Rotamers observed.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.51 – 7.38 (m, 5H, ArC*H*), 4.88 (d, $^2J_{HH}$ = 12.4, 1H), 4.83 (d, $^2J_{HH}$ = 11.8, 1H), 4.69 (d, $^2J_{HH}$ = 13.0, 1H), 4.61 (dd, $^2J_{HH}$ = 13.1, $^4J_{HH}$ = 2.1, 1H), 4.38 (dt, $^2J_{HH}$ = 11.8, $^4J_{HH}$ = 1.1, 1H), 4.27 (ddd, $^2J_{HH}$ = 11.8, $^4J_{HH}$ = 2.2, 1.2, 1H), 4.14 (d, $^2J_{HH}$ = 12.7, 0H), 4.09 (dd, $^2J_{HH}$ = 12.8, $^4J_{HH}$ = 1.9, 1H); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 156.1 (q, $^2J_{CF}$ = 38.3, R$_2$N*C*(O)CF$_3$), 156.1 (q, $^2J_{CF}$ = 38.3, R$_2$N*C*(O)CF$_3$), 130.4 (*C*$_g$), 129.2 (Ar*C*H), 129.2 (Ar*C*H), 127.9 (*C*$_d$), 127.7 (*C*$_d$), 127.0 (Ar*C*H), 127.0 (Ar*C*H), 122.8 (q, $^1J_{CF}$ = 278.5, C$_c$*C*F$_3$), 122.7 (q, $^1J_{CF}$ = 279.1, C$_c$*C*F$_3$), 115.9 (q, $^1J_{CF}$ = 287.6, R$_2$NC(O)*C*F$_3$), 115.9 (q, $^1J_{CF}$ =

287.6, $R_2NC(O)CF_3$), 64.4 (*C*$_b$), 64.3 (*C*$_b$), 62.5 (q, $^2J_{CF}$ = 37.3, *C*$_c$), 62.5 (q, $^2J_{CF}$ = 37.3, *C*$_c$), 58.5 (m, *C*$_a$), 57.7 (m, *C*$_a$), 56.2, (m, *C*$_a$), 55.4 (*C*$_a$); **^{19}F NMR** ($CDCl_3$, 377 MHz) δ –71.60 (C_cCF_3), –71.63 (C_cCF_3), –72.78 ($R_2NC(O)CF_3$), –72.81 ($R_2NC(O)CF_3$).

2,2,2-Trifluoro-1-(2-methyl-2-phenyl-1-oxa-5-azaspiro[2.3]hexan-5-yl)ethan-1-one, 253



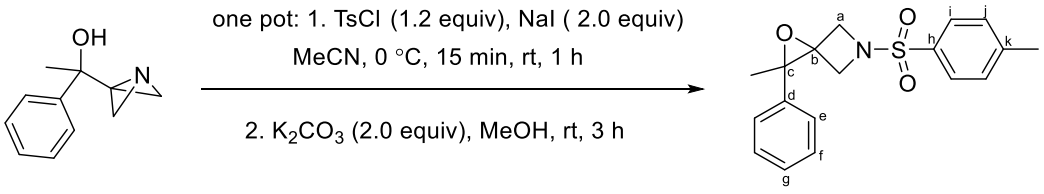
Prepared following general procedure H using the crude **197a** (0.25 mmol) and TFAA (40 μL, 1.2 equiv) in place of CbzCl. The crude reaction mixture was purified by flash column chromatography (98:2 → 85:15 pentane/acetone) to give **253** (26 mg, 38% yield) as a colourless oil. Ketone **241a** was also isolated (24 mg, 36% yield).

R$_F$ 0.49 (80:20 pentane/acetone); **IR** (film) ν_{max}/cm^{-1}: 2969, 1738, 1446, 1365, 1229, 1216; **HRMS** (ESI): Calcd. for $C_{13}H_{12}F3NO_3Na^+$ ([M+Na]$^+$) *m*/*z* 294.0712, found *m*/*z* 294.0723;

Rotamers observed.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.52 – 7.15 (m, 5H, ArC*H*), 4.71 (d, $^2J_{HH}$ = 11.1, 1H, C$_a$*H*), 4.63 (d, $^2J_{HH}$ = 11.2, 1H, C$_a$*H*), 4.51 (d, $^2J_{HH}$ = 12.7, 1H, C$_a$*H*), 4.47 (d, $^2J_{HH}$ = 12.1, 1H, C$_a$*H*), 4.39 (d, $^2J_{HH}$ = 12.0, 1H, C$_a$*H*), 4.24 (d, $^2J_{HH}$ = 12.3, 1H, C$_a$*H*), 4.10 (d, $^2J_{HH}$ = 11.1, 1H, C$_a$*H*), 3.93 (d, $^2J_{HH}$ = 12.2, 1H, C$_a$*H*), 1.69 (s, 6H, C*H*$_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 156.2 (q, $^2J_{CF}$ = 37.8, $CF_3C(O)NR_2$), 156.1 (q, $^2J_{CF}$ = 37.8, $CF_3C(O)NR_2$), 137.3 (*C*$_d$), 137.2 (*C*$_d$), 128.9 (Ar*C*H), 128.8 (Ar*C*H), 128.5 (Ar*C*H), 125.5 (Ar*C*H), 125.4 (Ar*C*H), 116.1 (q, $^1J_{CF}$ = 287.8, *C*F$_3$), 116.0 (q, $^1J_{CF}$ = 287.8, *C*F$_3$), 65.6 (q, $^4J_{CF}$ = 1.8, *C*$_b$), 63.2 (*C*$_c$), 63.18 (*C*$_c$), 58.3 (q, $^3J_{CF}$ = 2.0, *C*$_a$), 56.0 (*C*$_a$), 56.0 (*C*$_a$), 19.3 (*C*H$_3$), 19.3 (*C*H$_3$); **^{19}F NMR** ($CDCl_3$, 377 MHz) δ –72.72, –72.78.

2-Methyl-2-phenyl-5-tosyl-1-oxa-5-azaspiro[2.3]hexane, 254



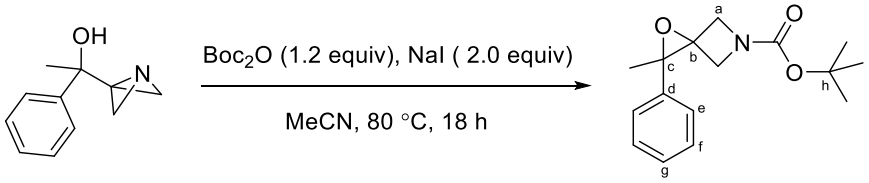
To a round bottom flask containing a mixture of crude **197a** (0.25 mmol, 1.0 equiv) and sodium iodide (75 mg, 0.5 mmol, 2.0 equiv) under an inert atmosphere was added anhydrous acetonitrile (2.5 mL). The flask was cooled to 0 °C and tosyl chloide (57 mg, 0.30 mmol, 1.2 equiv) was added with stirring. After 15 minutes at 0 °C, the reaction was warmed to room temperature and stirred for a further 1 hour. After this time, potassium carbonate (69 mg,

0.5 mmol, 2.0 equiv) was added followed by anhydrous methanol (2.5 mL) and the reaction stirred for 3 hours. Diethyl ether (10 mL) and saturated aqueous sodium bicarbonate solution (10 mL) were added, and the reaction mixture transferred to a separating funnel. The phases were separated, and the aqueous phase was extracted with diethyl ether (3 × 20 mL) and the combined organic phases were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography (99:1 → 80:20 pentane/acetone) to give **254** (72 mg, 87% yield) as a colourless oil that crystallised upon freezing.

R_F 0.56 (80:20 pentane/acetone); **IR** (film) ν_{max}/cm^{-1}: 2976, 2937, 1597, 1445, 1346, 1160; **HRMS** (APCI): Calcd. for $C_{18}H_{19}NO_3S^+$ ($[M+H]^+$) *m*/*z* 330.1158, found *m*/*z* 330.1160

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.72 (d, $^3J_{HH}$ = 8.2, 2H, 2 × C_i*H*), 7.37 (d, *J* = 8.2, 2H, 2 × C_j*H*), 7.34 – 7.24 (m, 3H, 2 × C_f*H*, C_g*H*), 7.12 – 7.03 (m, 2H, 2 × C_e*H*), 4.17 (d, $^2J_{HH}$ = 10.2, 1H, C_a*H*), 4.08 (d, $^2J_{HH}$ = 10.2, 1H, C_a*H*), 3.90 (d, $^2J_{HH}$ = 10.3, 1H, C_a*H*), 3.55 (d, $^2J_{HH}$ = 10.3, 1H, C_a*H*), 2.48 (s, 3H, ArC*H*$_3$), 1.53 (s, 3H, C*H*$_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 144.5 (*C*$_h$), 137.4 (*C*$_d$), 131.6 (*C*$_k$), 129.9 (2 × *C*$_j$), 128.5 (2 × *C*$_i$), 128.4 (2 × *C*$_f$), 128.1 (*C*$_g$), 125.4 (2 × *C*$_e$), 64.1 (*C*$_b$), 63.1 (*C*$_c$), 57.1 (*C*$_a$), 57.0 (*C*$_a$), 21.6 (Ar*C*H$_3$), 19.1 (*C*H$_3$).

***tert*-Butyl 2-methyl-2-phenyl-1-oxa-5-azaspiro[2.3]hexane-5-carboxylate, 255**



To a round bottom flask containing a mixture of crude **197a** (0.25 mmol, 1.0 equiv) and sodium iodide (75 mg, 0.50 mmol, 2.0 equiv) under an inert atmosphere was added anhydrous acetonitrile (2.5 mL). The flask was cooled to 0 °C and di-*tert*-butyl decarbonate (70 μL, 0.30 mmol, 1.2 equiv) was added with stirring and the reaction was then heated to 80 °C. After 18 hours, the reaction was cooled to room temperature before the addition of saturated aqueous sodium bicarbonate solution (10 mL) and diethyl ether (10 mL) were added, and the reaction mixture transferred to a separating funnel. The phases were separated, and the aqueous phase was extracted with diethyl ether (3 × 20 mL) and the combined organic phases were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography (99:1 → 90:10 pentane/acetone) to give **255** (39 mg, 57% yield) as a colourless oil.

R_F 0.56 (80:20 pentane/acetone); **IR** (film) ν_{max}/cm^{-1}: 2974, 2874, 1702, 1446, 1388, 1366, 1141; **HRMS** (ESI): Calcd. for $C_{16}H_{21}NO_3Na^+$ ($[M+Na]^+$) *m*/*z* 298.1414, found *m*/*z* 298.1411;

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35 (tt, $^3J_{HH}$ = 6.8, $^4J_{HH}$ = 1.6, 2H, 2 × C_fH), 7.34 – 7.26 (tt, $^3J_{HH}$ = 7.29, $^4J_{HH}$ = 1.5 1H, C_gH), 7.25 (m, 2H, 2 × C_eH), 4.27 (dd, $^2J_{HH}$ = 10.4, $^4J_{HH}$ = 1.6, 1H, C_aH), 4.18 (ddd, $^2J_{HH}$ = 10.4, $^4J_{HH}$ = 1.6, 0.8, 1H, C_aH), 4.04 (ddd, $^2J_{HH}$ = 10.5, $^4J_{HH}$ = 1.6, 0.8, 1H, C_aH), 3.68 (dd, $^2J_{HH}$ = 10.5, $^4J_{HH}$ = 1.6, 1H, C_aH), 1.65 (s, 3H, CH_3), 1.42 (s, 9H, $C_h(CH_3)_3$); **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 156.1 ($R_2NC(O)OR$), 138.3 (C_d), 128.6 (2 × C_f), 127.9 (C_g), 125.6 (2 × C_e), 80.1 (C_h), 66.0 (C_b), 62.8 (C_c), 55.9 (br., 2 × C_a), 28.4 ($C_h(CH_3)_3$), 19.4 (CH_3).

7. References

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